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VOLUME 70

BALTIMORE  
THE WILLIAMS & WILKINS COMPANY  
1953





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# SOME NEW PERSPECTIVES IN RENAL PHYSIOLOGY

A. V. WOLF

*Department of Physiology and Pharmacology, Albany Medical College, Albany, N. Y.*

It has been my great pleasure to be invited to these meetings, to visit with you these past few days, and to enjoy that hospitality for which urologists are renowned. And I am, of course, honored that you have asked me to deliver your Ballenger lecture. It is with some regret, therefore, that I have chosen to talk to you today about a few matters which currently interest practically no one in clinical medicine. However, the aspect of things changes with time, and with that conviction I hope to justify a discussion of some of the odd pursuits of renal physiologists.

## A BIT ON WATER BALANCE

The amount of water in the body is, as you know, rather constant from day to day in a healthy person. This has something to do with the fact that the kidneys help to get rid of excesses, but that organ cannot of itself replenish a deficit of water. Although casual reflection tells us that intake must importantly affect the amount of water in the body, it requires something of the instincts of a book-keeper, which not all of us have, to appreciate fully the cold beauty of the relation

$$\text{Balance} = \text{Gain} - \text{Loss.}$$

It has been said that in the infant with only fluid intakes, thirst is a substitute for hunger, presiding over alimentation.<sup>1</sup> If so, "gain" and thence "loss" in the balance equation is more closely identified with thirst than in the adult. Yet a study of thirst in the adult is a study of the headwaters of the urine, as it were, and remains a good thing to undertake if we wish to keep perspective on the meaning of the urine flow. Let us work into this subject gradually, first by following the course of an intravenous injection of a liter load of 5 per cent glucose solution.

Quickly mingling with the blood and other body fluids, the glucose is removed by metabolic processes, leaving in effect a load of distilled water. This water load dilutes the dissolved materials of the body, lowering their effective osmotic pressure, especially that of sodium and chloride. Verney's<sup>2</sup> painstaking researches have led him to postulate the existence of tiny, vesicular organelles, lying in the bed of the internal carotid artery in the central nervous system, which respond to this dilution by osmotic swelling. These hypothetical osmometers might behave as

Condensed from third annual Edgar Ballenger Memorial Lecture delivered April 5, 1952, Boca Raton, Florida, before the Southeastern Section of the American Urological Association.

Present address: Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D. C.

<sup>1</sup> Rullier: *Soif. Dictionaire des Sciences Médicales*, 51: 448-490, 1821. Paris: Panckoucke, Éd.

<sup>2</sup> Verney, E. B.: The antidiuretic hormone and the factors which determine its release. *Proc. Roy. Soc., London*, s. B. 135: 25-106, 1947.

stretch receptors for afferent nerves, impulses along which could reflexly cause the posterior pituitary gland to reduce below normal its rate of secretion of anti-diuretic hormone. The result of this, following the short time during which already circulating hormone is being removed by organs such as the liver, would be a decreased tubular reabsorption of water by the renal tubules, and a consequent diuresis. If all this is so, we have a simple explanation of the water diuresis, including its latent period, which follows drinking or intravenous infusion of salt-free water.

The urine formed in water diuresis, which has been thought of as a sort of physiological diabetes insipidus, is characteristically more dilute than normal plasma not only with respect to nonprotein solids but with respect to effective osmotic pressure which is largely due to salts. The effect of removing from the body a fluid containing relatively more water than salt is to make the residual (diluted) body fluids more concentrated. As the concentration of salts in these body fluids returns toward normal, the "water removal" reflex, including osmoreceptive cells on the afferent, and neurohypophyseal cells on the efferent sides, becomes something of a "water conservation" reflex. Antidiuretic hormone again circulates, renal tubules reabsorb water as before, and urine flow returns to adiuretic levels.

This theory does not tell us why a liter load of normal saline is excreted, if it causes no appreciable change in the effective osmotic pressure of body fluids. True, in man, a liter of saline is usually excreted more slowly than a liter of water, but this is not always the case as one discovers in the course of many such tests. It is even less true in the dog where, although one may still distinguish the diuretic effects of glucose solution from those of normal saline, the differences are usually less pronounced. Anyway, the theory does not cover this point.

In my opinion<sup>3</sup> latter day nephrodynamic studies based on inulin or similar clearances make little sense of this problem. Without laboring the point that the experimental error in the determination of the glomerular filtration rate often swallows up the very changes one might wish to delineate, there is the more important consideration that the best theory we have of maximum tubular reabsorptive capacities (Tm) as applied to sodium and chloride<sup>4-6</sup> has not been confirmed for having any extensive, physiologic, regulatory role.<sup>7-15</sup> But the theory has lots of magnetism because of its simple, mechanistic features; and the logico-

<sup>3</sup> Wolf, A. V.: *The Urinary Function of the Kidney*. New York: Grune & Stratton, 1950.

<sup>4</sup> Wesson, L. G., Jr. and Anslow, W. P., Jr.: Excretion of sodium and water during osmotic diuresis in the dog. *Am. J. Physiol.*, **153**: 465-474, 1948.

<sup>5</sup> Smith, H. W.: *The Kidney: Structure and Function in Health and Disease*. New York: Oxford Univ., 1951.

<sup>6</sup> Ladd, M.: Renal excretion of sodium and water in man as affected by prehydration, saline infusion, pitressin and thiomerin. *J. Applied Physiol.*, **4**: 602-619, 1952.

<sup>7</sup> Hare, R. S., Hare, K. and Phillips, D. M.: The renal excretion of chloride by the normal and by the diabetes insipidus dog. *Am. J. Physiol.*, **140**: 334-348, 1943.

<sup>8</sup> Ekehorn, G.: XI. Renal thresholds. General remarks. *Acta med. Scandinav.*, **124**: 494-510, 1946.

<sup>9</sup> Mudge, G. H., Foulks, J. and Gilman, A.: Effect of urea diuresis on renal excretion of electrolytes. *Am. J. Physiol.*, **158**: 218-230, 1949.

<sup>10</sup> Wolf, A. V. and Ball, S. M.: Effect of intravenous sodium sulfate on renal excretion in the dog. *Am. J. Physiol.*, **160**: 353-360, 1950.

<sup>11</sup> Black, D. A. K., Platt, R. and Stanbury, S. W.: Regulation of sodium excretion in normal and salt-depleted subjects. *Clin. Sc.*, **9**: 205-221, 1950.

psychic law of parsimony which rules over scientific hypotheses justifies its wide influence in recent researches.

To return to our considerations of water balance, let us suppose the postpituitary theory adequate to account for removal of positive loads of water. How about negative loads? Verney's theory accounts nicely for the oliguresis which sets in following ordinary dehydration. Here effective osmotic pressure of body fluids is greater than normal; shrinking osmoreceptors call not for decreased but for increased secretion of antidiuretic hormone; and only that small, obligatory urine flow, consistent with the removal of solutes demanding excretion, obtains. Still, water continues to leave the body, even if more slowly, and water deficits grow. Then thirst appears. A thirsty garter snake, rabbit, or dog would in a few minutes of access to water drink back an amount approximately equal to its deficit.<sup>16</sup> A man takes somewhat longer. What regulates the intake in any case? An old view, still advocated in some quarters, has the dryness of the mouth as the stimulus to drink, and absolute or relative dehydration is known to result in scanty salivary secretion which presumably favors irritation of the mouth and throat. Unfortunately the dry mouth theory<sup>17</sup> is mainly qualitative and does not account well for the metering of water intake to body needs. It certainly does not account for the sudden onset of thirst when a salty anchovy is taken and saliva flows profusely. The more widely considered cellular dehydration theory,<sup>18,19</sup> which correlates thirst with the effective osmotic pressure of body fluids, lends itself to quantitative analysis of thirst, but without refinement it is inadequate to account for such things as thirst in hyposalemia (hyponatremia),<sup>20-22</sup> or the curious polydipsia which arises from enforced polyposia.<sup>23-25</sup> By injecting vari-

<sup>12</sup> Tarail, R., Seldin, D. W. and Goodyer, A. V. N.: Effects of injection of hypertonic glucose on metabolism of water and electrolyte in patients with edema. *J. Clin. Investigation*, **30**: 1111-1119, 1951.

<sup>13</sup> Lewis, J. M., Jr., Buie, R. M., Sevier, S. M. and Harrison, T. R.: The effect of posture and of congestion of the head on sodium excretion in normal subjects. *Circulation* **2**: 822-827, 1950.

<sup>14</sup> Viar, W. N., Oliver, B. B., Eisenberg, S., Lombardo, T. A., Willis, K. and Harrison, T. R.: The effect of posture and of compression of the neck on excretion of electrolytes and glomerular filtration: further studies. *Circulation* **3**: 105-115, 1951.

<sup>15</sup> Lombardo, T. A., Eisenberg, S., Oliver, B. B., Viar, W. N., Eddleman, E. E., Jr. and Harrison, T. R., Effects of bleeding on electrolyte excretion and on glomerular filtration. *Circulation*, **3**: 260-270, 1951.

<sup>16</sup> Adolph, E. F.: *Physiological Regulations*. Lancaster: Cattell, 1943.

<sup>17</sup> Cannon, W. B.: The physiological basis of thirst. *Proc. Roy. Soc., London*, s. B. **90**: 283-301, 1918.

<sup>18</sup> Gilman, A.: The relation between blood osmotic pressure, fluid distribution and voluntary water intake. *Am. J. Physiol.*, **120**: 323-328, 1937.

<sup>19</sup> Dill, D. B.: *Life, Heat, and Altitude*. Cambridge: Harvard, 1938.

<sup>20</sup> Elkhinton, J. R. and Squires, R. D.: The distribution of body fluids in congestive heart failure. I. Theoretic considerations. *Circulation*, **4**: 679-696, 1951.

<sup>21</sup> Holmes, J. H. and Cizek, L. J.: Observations on sodium chloride depletion in the dog. *Am. J. Physiol.*, **164**: 407-414, 1951.

<sup>22</sup> Cizek, L. J., Semple, R. E., Huang, K. C. and Gregersen, M. I.: Effect of extracellular electrolyte depletion on water intake in dogs. *Am. J. Physiol.*, **164**: 415-422, 1951.

<sup>23</sup> Regnier, A.: Ueber den Einfluss diätetischer Massnahmen auf das osmotischer Gleichgewicht des Blutes beim normalen Menschen. *Ztschr. f. exper. Path. u. Therap.*, **18**: 139-164, 1916.

<sup>24</sup> Kunstmann, D.: Über die Wirkung der Zufuhr grosser Wassermengen auf den Organismus. *Arch. f. exper. Path. u. Pharmacol.*, **170**: 701-718, 1933.

<sup>25</sup> Holmes, J. H. and Montgomery, A. V.: Physiological changes induced by high fluid intakes. *Federation Proc.*, **10**: 66, 1951.



ously concentrated salt solutions in men until thirst just appeared, and by calculating the resulting degree of general cellular dehydration on an osmometric basis, it has been found that cells will lose up to 1 to 2 per cent of their fluid volume, whereupon the thirst threshold is reached.<sup>26</sup> Now Verney calculated that his pituitary osmoreceptors responded to changes in effective osmotic pressure of the order of 1 to 2 per cent. This coincidence was partly responsible for the proposal that thirst actually has its origin in osmoreceptors of the same genus as Verney's. Make no mistake, however. Anatomically, both pituitary osmoreceptors and thirst osmoreceptors are presently hypothetical, notwithstanding repeated accounts in learned journals which take these receptors for granted. It is difficult to refrain from casting one's lot with that of a neat idea, but sober fact is a better canon of verity than that of the Bellman in *The Hunting of the Snark*.\*

If we are willing to recognize for the oversimplification it is that thirst must be due solely either to a "dry mouth" or to "cellular dehydration," we may go on to a more sophisticated view of dipsogenic and antidipsic influences. Suppose there actually were osmoreceptors for thirst somewhere, perhaps in the central nervous system. In the course of ordinary, general tissue dehydration, not only would these receptors lose water, but tissues in the oral cavity would lose likewise. Few physiological associations would be more likely to set into a conditioned reflex than these. It may be that local dryness of the mouth and throat, or osmotic stimulation of their membranes, acts merely as a conditioned stimulus. This might excite sensory nerves joining a primitive thirst reflex having primary osmoreceptors and afferent nerves deep in body tissues such as the central nervous system. The reflex would terminate in effectors which cause the taking of water. This concept of thirst<sup>3</sup> rescues the best features of both the cellular dehydration and the dry mouth theories and discovers advantages beyond this. It accounts for the sudden onset of thirst, when sweet chocolate is chewed, as a conditioned thirst reflex. Here the mouth is moist but presumably there is osmotic stimulation of its membranes. General cellular dehydration cannot be involved in so short a latent period and, with or without the taking of water, the thirst disappears shortly after the oral stimulation is removed. The "conditioned reflex" theory, moreover, is susceptible of extension and amplification in the light of other observations. It also permits of being tested in new experimental ways but these matters cannot be pursued here.

Let us remark on the previously noted thorny aspects of the thirst problem: first, the phenomenon of thirst in the presence of hyposalemia and, second, the

<sup>26</sup> Wolf, A. V.: Osmometric analysis of thirst in man and dog. *Am. J. Physiol.*, **161**: 75-86, 1950.

\* "Just the place for a Snark!" the Bellman cried,

As he landed his crew with care;  
Supporting each man on the top of the tide  
By a finger entwined in his hair.

"Just the place for a Snark! I have said it twice:  
That alone should encourage the crew.  
Just the place for a Snark! I have said it thrice:  
What I tell you three times is true."

induction of thirst by forced, sustained water intakes. Of the latter, not too much is known beyond the reports of Regnier,<sup>23</sup> Kunstmann,<sup>24</sup> and Holmes and Montgomery.<sup>25</sup> Kunstmann drank up to 18 liters of water per day for four months and succeeded thereby in developing intense thirst which forced him to get up at night to drink. Not before several days following cessation of intensive drinking did the thirst abate\*.

The existence of thirst in hyposalemia seems at first a negation of the cellular dehydration theory but this is not necessarily the case. This theory (or its osmoreceptive offspring) tells us to expect thirst when so and so much tissue dehydration sets in. But it does not tell us that thirst cannot co-exist with cellular hydration. Within narrow limits, cellular hydration does seem properly to be an antidiptic influence but McCance<sup>27</sup> depleted human subjects of salt and noted that the hyposalemia was associated with, among other things, a flavor-sense aberration sometimes mistaken for thirst. Water was desired and drunk but gave no relief. Apparently paradoxically, taking salt relieved the desire for water and this could be followed by "real" thirst.† The probable cellular hydration in hyposalemia should on the face of things give rise to anything but thirst. Yet thirst may occur. Some hold<sup>20</sup> that "accommodation" of cells to the hyposalemic level sets in so that elevation of saline osmotic pressure with respect to the hyposalemic baseline would lead to thirst in accord with osmoreceptive theory. Such accommodation has also been postulated for the antidiuretic hormone osmoreceptors.<sup>2, 5</sup> And so it may be. But there are weaknesses in this view, not the least of which is the fact that accommodation in reverse is relatively unknown; that is, one does not apparently accommodate so as to have no thirst in a hypersalemic setting. The desert habitué calls for his water at pretty much the normal threshold and no success attends training with an eye to getting along with large deficits of body water.<sup>26</sup> On the other hand, however, accommodation may be more characteristic of "disease."

If we are to have osmoreceptors for thirst that stimulate afferent nerves when they shrink in hypertonicity, why not when they stretch in hypotonicity? Could this account for thirst in hyposalemia which cannot be sated by water but only by salt?

Having scratched the topics of diuresis and thirst, I should like now to derive a curious relationship between ordinary thirst and urine flow, invoking no real or fancied physiologic mechanisms, no nephrodynamics or cellular kinetics, nor any physical theory at all. Consider in a purely abstractive way a man starting out with no salt or water excesses or deficits, who simply sits, generating urine

\* Kunstmann's findings— an 8 day latent period before onset of thirst, an elevation of serum chloride and osmotic pressure during thirst, persistence of thirst after termination of forced drinking, and obstipation— may be explicable if a state of real but temporary diabetes insipidus could be caused by some "disuse atrophy" of the posterior pituitary in the face of steady water loading. There are some inconsistencies in this view, but we desist now for it takes us too far afield.

<sup>27</sup> McCance, R. A.: Experimental sodium chloride deficiency in man. *Proc. Roy. Soc., London*, s. B. 119: 245-268, 1936.

† "Real" thirst in this case is thirst which can be satiated by water, but how far satiety can serve a crucial definition is moot.

<sup>26</sup> Adolph, E. F. and associates: *Physiology of Man in the Desert*. New York: Interscience 1947.

and throwing off pulmocutaneous water vapor as is his wont. Under these conditions, where urine production gradually falls off with progressive dehydration, the osmotic pressure of the urine tends to become greater than that of the plasma. The effect of removing from the body a volume of fluid whose osmotic pressure is greater than that of the fluids remaining behind is to cause the remaining fluids to become more dilute. While this constitutes an antidipsic influence, the pulmocutaneous removal of water in excess of salt tends to concentrate the body fluids with respect to osmotic pressure. Here we have a dipsogenic influence. We know these two factors are not balanced because thirst eventually supervenes. It is easy to show by "lower mathematics" that, if thirst is to be precipitated under these conditions, a necessary inequality exists physiologically between the rate of insensible water loss and the rate of urine formation. So long as the effective osmotic pressure of the urine is two or more times that of the plasma, the insensible loss exceeds the rate of obligatory urine flow.<sup>3</sup> Contained here is the odd implication that in any mammal—mouse, man, or elephant—undergoing ordinary dehydration this inequality should obtain.

It is in considerations like the above, employing analysis, integration, and abstraction that one begins to catch a glimpse of the subtleties of water balance. I think that too few investigators today accept the "realities" of abstractive or mathematical theories in physiology. They are inclined to dismiss relations of these sorts as "empirical," reserving for the term "theoretical" only those relations which have crudely obvious physical determinants.\*

#### VOLUME REGULATION

Fifteen years ago orthodox renal physiologists viewed anyone who proclaimed the kidney to be an organ of volume regulation as a visionary of the worst kind. Today the emphasis has so far shifted that some physiologists, relaxing with a science-fiction story about a mountainous mass of protoplasm able to devour whole cities, would instantly perceive that a problem of volume imbalance must be at issue.

The clinician is most likely to think of volume regulation in terms of edematous states, but these "perversions" of volume regulation, for all their practical importance, are only small parts of a pervasive physiologic problem. One side of this problem is set forth by the sort of question asked earlier. "Why should a liter load of saline of the same composition as plasma ever be excreted if it pro-

\* Poincaré<sup>33</sup> has treated this vital point. "Suppose," he says, "we have before us any machine; the initial wheel work and the final wheel work alone are visible, but the transmission, the intermediary machinery by which the movement is communicated from one to the other, is hidden in the interior and escapes our view; we do not know whether the communication is made by gearing or by belts, by connecting-rods or by other contrivances. Do we say that it is impossible for us to understand anything about this machine so long as we are not permitted to take it to pieces? You know well we do not, and that the principle of the conservation of energy suffices to determine for us the most interesting point. We easily ascertain that the final wheel turns ten times less quickly than the initial wheel, since these two wheels are visible; we are able thence to conclude that a couple applied to the one will be balanced by a couple ten times greater applied to the other. For that there is no need to penetrate the mechanisms of this equilibrium and to know how the forces compensate each other in the interior of the machine; it suffices to be assured that this compensation can not fail to occur."

duces no concentration changes in the plasma?" This question is the more puzzling so long as one refuses to admit that the body or the kidney can respond physiologically to undo loads of volume independently of loads of concentration. It remains puzzling to those students of nephrodynamics who do not emancipate themselves from the belief that inulin clearances must hold the answer.

We have not the time to entertain this fascinating topic now, nor to review the spate of recent papers on volume receptors. It is enough to note that various workers postulate such receptors, preferably in the cephalad portion of the body.<sup>17-19, 21-23</sup> When a person lies down he shows recumbence diuresis, perhaps because body fluid shifts toward cephalic volume receptors. The removal of edema from some patients following bed rest alone has even been attributed to diuresis following stimulation of such volume receptors. And in the recumbent position, intravenous saline is said to be more diuretic than in the sitting position. The existence of volume receptors has been tested, for example, by the use of an occlusion cuff placed around the neck of a sitting victim, thereby congesting the blood in the head and simulating the recumbent position in this regard.<sup>12</sup> Unfortunately, indirection of this sort appears to be essential inasmuch as the direct test of cutting off a patient's head and comparing the effects with a control is proscribed and, indeed, naive. As that estimable *savant*, Claude Bernard observed, a good physiologist must have a feeling for the complexity of things.

I am presently conducting equally indirect tests of volume regulation and regret being unable at this time to pass on to you definitive results. My studies make use of statistical correlation of changes in salt excretion with the distortion of extracellular and intracellular fluid compartments. The distortion in this case is an algebraic summation of changes in extracellular volume (where an increase is called  $+$ ) and in intracellular volume (where a decrease is called  $+$ ). Distortions caused by loads of salt and water are calculated by means of osmometric equations, and the underlying idea is that if the kidney regulates volumes, its excretion of salt will be highly correlated with the osmotic volume imbalances produced by any combination of positive or negative loads of salt and/or water. The nephrodynamic purist might be quick to note that these correlation curves fit their graphed points only better than the constellations describe their signs of the zodiac. But let him remember that various subject matters in the universe have sundry but characteristic kinds of correlation with other subject matters and, in any case, correlations of salt excretion with distortions are better than those of salt excretion with salt load. This is a significant physiologic fact which is not predicted quantitatively by current theories of filtration and tubular reabsorption.

<sup>22</sup> Lewis, J. M. and Sevier, S. M.: Some factors influencing sodium excretion. *Am. J. Med.*, 7: 248, 1949.

<sup>23</sup> Welt, L. G. and Orloff, J.: The effects of an increase in plasma volume on the metabolism and excretion of water and electrolytes by normal subjects. *J. Clin. Investigation* 30: 751-761, 1951.

<sup>21</sup> Strauss, M. B., Davis, R. K., Rosenbaum, J. D. and Rossmesl, E. C.: "Water diuresis" produced during recumbency by the intravenous infusion of isotonic saline solution. *J. Clin. Investigation*, 30: 862-868, 1951.

## THE ARTIFICIAL KIDNEY

The technique and science of hemodialysis contribute importantly to new perspectives in renal physiology.<sup>32</sup> This is not because of any similarity between the diffusion-filtration processes of the artificial kidney and the filtration-reabsorption-secretion processes of the natural kidney, but rather because excretion and retention with the former can be accurately controlled for many different materials, simultaneously, at the choosing of the hemodialyst. He can reduce the level of plasma potassium, for example, below that to which a natural kidney could, and can study the effects of low levels of other materials in the blood whose concentrations in disease only rise. He can now, and should in the future even better, control water balance for particular purposes. He can search for the unknown etiologic, and possibly specific, agent or agents of uremia directly by appropriately designed differential dialyses. And anyone who has watched "certain" uremic death take a holiday after a six hour blood rinsing will have a new perspective in renal physiology.

In the past investigators have derived valuable information by using "perfused" kidneys and "isolated" kidneys. These methods are powerful but not always productive of reliable inference as to physiologic processes. The "artificial" kidney adds a new method with far-reaching possibilities.

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We have now considered, although unevenly, three "new perspectives" in renal physiology: 1) in the possibilities inhering in integration and analysis of fluid intake and output, that is, in the subtleties of water balance; 2) in the renal regulation of body volume considered independently of nephrodynamics; and 3) in the new techniques of hemodialysis. Let me spare you further summary and rather conclude in a philosophic vein.

In recent years there has been a remarkable but unhappy uniformity of methods used to study mammalian kidneys in action. Few question the immense power of these methods, or undervalue the insight which—to take an important example—the probable determination of the rate at which glomerular juice is squeezed into tubules gives into fundamental mechanisms. But today "filtration," "blood flow," and "clearance" have become gods of renal physiology, and too many are their prophets. I think that if we can learn anything from the long history of ill-starred theories in renal physiology it is that we should not invoke these or any other deities of the vital yellow fluid, alone. Some would have us believe the proper theoretic basis for kidney science lies only in these ideas and that others must be empirical. But to insist on the virtue of the physical, and on the futility of the abstractive, is manifestly to mistake the nature of scientific theories and to preclude us from attaining to new perspectives in renal physiology.

<sup>32</sup> Wolf, A. V.: *The artificial kidney*. Science, **115**: 193-199, 1952.

<sup>33</sup> Poincaré H.: *The Foundation of Science*. New York: Science Press, 1913, pp. 299-300.

# CLINICAL DIAGNOSIS OF TUMORS OF ADULT RENAL PARENCHYMA

EDGAR BURNS

*From the Department of Urology, Ochsner Clinic and the Division of Urology, Tulane University of Louisiana, School of Medicine, New Orleans*

A discussion of the problems involved in the clinical diagnosis of tumors of the adult renal parenchyma was stimulated by a review of statistical reports from several leading medical centers which showed that not more than 50 per cent of patients were alive three years after nephrectomy, less than 40 per cent survived five years and less than 30 per cent were alive and free from recurrence at the end of ten years. These figures indicate that the tumor had spread beyond the confines of the kidney in more than 70 per cent of cases at the time operation was performed. It has long been recognized that early diagnosis of renal tumors and removal of the kidney before metastasis occurs offer the only hope of cure. Recognition of renal tumors is presently based upon correlation of symptoms with the results obtained from the presently available diagnostic procedures. Unilateral renal disease responds favorably to surgical excision and cure should be effected if nephrectomy is performed while the disease is still confined to the kidney. However, at present less than one-third of patients with renal tumors are being cured; this means that better methods of earlier recognition must be provided if more patients are to be cured.

The triad of symptoms long recognized as suggestive evidence of renal tumors are hematuria, pain and a mass in the side. Gross hematuria is the initial symptom in not more than half of the cases. It occurs only after the tumor has broken through into the collecting system, and since many tumors remain encapsulated for a long time, the initial appearance of blood in the urine does not necessarily indicate an early stage of the disease. On the other hand, the significance of microscopic hematuria should perhaps be given more emphasis. Blood may appear in the urine as a result of a variety of lesions in any part of the urinary tract, the two most important of which are cancer and tuberculosis. These obviously should be eliminated first before consideration is given to less important lesions. The too frequent tendency to minimize the significance of the initial passage of blood in the urine is probably one of the greatest contributing factors to the present delay in recognizing renal tumors. Although it should by no means be interpreted as indicative of an early stage of the disease, blood in the urine should mean cancer until appropriate investigation proves that it does not exist. Such studies imply that interval follow-up examinations are imperative if a gross lesion is not found upon the initial examination.

Pain is said to be an initial symptom of renal tumors in approximately 30 per cent of cases. Three reasons are assigned for its occurrence. The first is increased intrarenal pressure from growth of the tumor within the renal capsule or pressure on surrounding structures. Dull and aching in character, such pain is usually lo-

Past president's address read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 6, 1952.

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*From the Department of Urology, Ochsner Clinic and the Division of Urology, Tulane University of Louisiana, School of Medicine, New Orleans*

A discussion of the problems involved in the clinical diagnosis of tumors of the adult renal parenchyma was stimulated by a review of statistical reports from several leading medical centers which showed that not more than 50 per cent of patients were alive three years after nephrectomy, less than 40 per cent survived five years and less than 30 per cent were alive and free from recurrence at the end of ten years. These figures indicate that the tumor had spread beyond the confines of the kidney in more than 70 per cent of cases at the time operation was performed. It has long been recognized that early diagnosis of renal tumors and removal of the kidney before metastasis occurs offer the only hope of cure. Recognition of renal tumors is presently based upon correlation of symptoms with the results obtained from the presently available diagnostic procedures. Unilateral renal disease responds favorably to surgical excision and cure should be effected if nephrectomy is performed while the disease is still confined to the kidney. However, at present less than one-third of patients with renal tumors are being cured; this means that better methods of earlier recognition must be provided if more patients are to be cured.

The triad of symptoms long recognized as suggestive evidence of renal tumors are hematuria, pain and a mass in the side. Gross *hematuria* is the initial symptom in not more than half of the cases. It occurs only after the tumor has broken through into the collecting system, and since many tumors remain encapsulated for a long time, the initial appearance of blood in the urine does not necessarily indicate an early stage of the disease. On the other hand, the significance of microscopic hematuria should perhaps be given more emphasis. Blood may appear in the urine as a result of a variety of lesions in any part of the urinary tract, the two most important of which are cancer and tuberculosis. These obviously should be eliminated first before consideration is given to less important lesions. The too frequent tendency to minimize the significance of the initial passage of blood in the urine is probably one of the greatest contributing factors to the present delay in recognizing renal tumors. Although it should by no means be interpreted as indicative of an early stage of the disease, blood in the urine should mean cancer until appropriate investigation proves that it does not exist. Such studies imply that interval follow-up examinations are imperative if a gross lesion is not found upon the initial examination.

*Pain* is said to be an initial symptom of renal tumors in approximately 30 per cent of cases. Three reasons are assigned for its occurrence. The first is increased intrarenal pressure from growth of the tumor within the renal capsule or pressure on surrounding structures. Dull and aching in character, such pain is usually lo-

Past president's address read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 6, 1952.

cated in the renal area but may be referred to the upper abdominal region. The second reason for pain is increase in the weight of the renal mass; such patients complain of increased discomfort when up and about because of added drag on the renal pedicle. The third cause of pain is passage of a blood clot down the ureter during a period of gross hematuria. This pain simulates renal colic. With the possible exception of the latter, pain probably is rarely an early symptom of renal tumor. Many lesions produce discomfort in the renal area and if hematuria has not occurred, there is too frequently a tendency even among urologists to fail to make the necessary studies to establish the presence or absence of a malignant lesion.

A *mass in the side* is the initial symptom in a small group of patients. The majority of these have tumors of low grade malignancy that grow slowly and may remain encapsulated for a long time. In thin patients a mass in the side will not long escape detection, but in those with a thick layer of abdominal fat the tumor may escape notice unless there are other associated symptoms. A mass, therefore, is not an early clinical manifestation of the disease.

In some of these patients metastatic lesions, usually in the lungs or bones, may be the first indication of malignancy. General surgeons are now alert to the frequency with which carcinoma is found within the thoracic cage, and are aggressive in its treatment. The metastatic character of some renal tumors should be emphasized and for this reason definitive treatment should not be carried out until the urinary tract has been completely investigated to eliminate the possibility of its being the primary source of the pulmonary lesion. In extremely rare cases, the pulmonary lesion may represent solitary metastasis; in such an instance nephrectomy and pneumonectomy may seem justifiable. However, in the majority of cases the presence of metastatic lesions is a contra-indication to nephrectomy.

Not infrequently, a soft tissue shadow will be seen in the retroperitoneal area in roentgenograms of the gastro-intestinal tract in patients with no symptoms suggestive of renal disease. Since renal tumors represent the commonest retroperitoneal mass, such cases should be studied from that standpoint before surgical exploration. Surgical errors due to failure to do this are not infrequent. Since the diagnosis of renal tumor is based upon correlation of clinical symptoms and urologic findings, the accuracy of the conclusions reached will be directly proportional to proper evaluation of the former and correct interpretation of the latter. The information obtained from the present methods of study of the urinary tract is usually sufficient to establish a positive diagnosis of renal tumor preoperatively.

The *plain roentgenogram* will indicate an increase in the size of the renal mass or a soft tissue shadow in the renal area. *Excretory urograms* as a preliminary to instrumental studies will indicate the location of the lesion in the majority of cases if the renal function is good. *Cystoscopy* and *retrograde pyelograms* are required in all cases, not only to obtain further confirmation of the presence of the renal lesion and perhaps suggest its character but also to eliminate the possibility of other associated lesions. *Retrograde pyelograms* should always be done bilater-

ally and in both the prone and upright positions in order to determine fixation of the affected side, which is a poor prognostic sign. A lateral pyelogram will give additional information on the side of the suspected lesion. The correct performance and interpretation of the pyelogram constitute one of the most important steps in the diagnosis of renal tumors. Among the most frequent changes in the pyelogram are compression and elongation of one or more calyces, with an abnormal ending, and disturbance of the relation of one calyx to another. One or more calyces may be completely obliterated. The renal pelvis is usually distorted. The ureteropelvic junction may be obstructed. Calcification may be present and the renal shadow is enlarged and its outline irregular. Similar changes in the pyelogram may be produced by a solitary cyst, from which tumors must always be differentiated.

The responsibility of interpreting the urograms should not be placed upon the radiologist. This is the primary duty of the urologist. With the advantage of the history and results of physical examination, he is in a better position to detect minor deviations from normal in the urogram. Failure to recognize early changes in the pyelogram is one of the commonest causes of failure to diagnose these tumors early.

Other diagnostic aids in the recognition of renal tumors are perirenal insufflation, exfoliative cytology and aortography. Carelli<sup>1</sup> in 1921 first described the technique of *perirenal insufflation* for clearer visualization of renal outlines, the adrenal glands and other retroperitoneal structures. Fifteen years later Cahill<sup>2</sup> called attention to its value in certain types of retroperitoneal lesions. If correctly performed, perirenal insufflation should indicate whether the soft tissue shadow is in the kidneys, the adrenals or adjacent structures. The procedure is not without danger. Air embolism is always a possibility, especially in patients with large tumors and large veins running in the perirenal area. Bending exercises immediately after insufflation may predispose to embolism. We saw one patient who went to the gymnasium shortly after perirenal insufflation had been performed, and, by exercising, diffused the air into the mediastinum and tissues of his neck. The air is usually absorbed in three to five days. Of course, the different types of lesions of the renal parenchyma cannot be determined by this procedure, but the location of the mass in the kidney, the adrenal or adjacent structures can be established.

*Exfoliative cytology*, as developed by Papanicolaou, offers a possibility of early recognition of malignancy of the urinary tract before the lesion becomes large enough to produce gross changes in the urogram. This method is perhaps less applicable to tumors of the renal parenchyma than it is to those of the renal pelvis and other parts of the urinary tract where cells are thrown off in greater numbers. On the other hand, once a parenchymal tumor has invaded the collecting system to the extent that hematuria occurs, cells of diagnostic significance may be found in the urine during this period. This test has significance only if

<sup>1</sup> Carelli, H.: Artificial emphysema for roentgenography of the kidney. Bull. et mem. Soc. med. d. hop. de Par. 45: 1409, 1921.

<sup>2</sup> Cahill, G. F.: Air injections to demonstrate adrenals by x-ray. J. Urol., 34: 238-243 1935.

the results are positive. It should be emphasized that the value of this procedure is directly proportional to the ability of the individual performing it. It is understandable that a diagnosis of malignancy would be harder to make from cells collected from the urinary sediment than it would be from an adequate biopsy obtained from the tumor. This test, therefore, should always be done under the direction of a well trained pathologist who is thoroughly familiar with the technique.

*Aortography* is the most recent and perhaps the most accurate adjunct in the differential diagnosis of a space-occupying lesion in the renal parenchyma. The technique has now been sufficiently developed so that it can be performed with

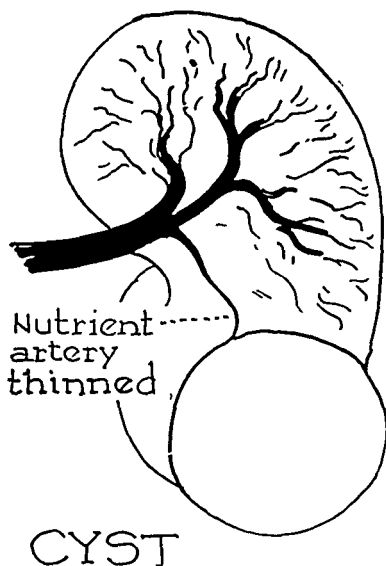


FIG. 1

a minimal risk of complications. It is indicated in any patient in whom the standard urographic procedures yield inconclusive information. For example, a small, questionable deformity in the pyelogram may be shown to be nothing more than a variation from the normal pattern or it may prove the presence of an early tumor. Aortography is helpful in determining the cause of irregularities in the renal outline, not necessarily producing pyelographic deformity. The value of aortography in the solution of this type of problem was recently demonstrated in the case of a 51 year old man admitted to the medical service complaining of headaches. In the course of routine studies a slight irregularity was noted in the renal outline, which did not produce any disturbance of the normal pattern in either the intravenous or retrograde pyelograms. An aortogram, however, demonstrated the presence of a tumor 3 cm. in diameter in the renal cortex. When the kidney was removed, it was found that the tumor already had invaded the renal vein. The nature of irregularities which occur in conjunction with, but not necessarily a part of, other renal lesions may be determined by aortography. This was recently illustrated in a patient with left calculous pyonephrosis and an irregu-

larity in the outline of the right kidney with a minor disturbance in the calyceal pattern. The aortogram proved this to be a cyst, so that the calculous pyonephrosis could be removed without concern as to whether or not the lesion in the right kidney represented a tumor. Aortography has proved valuable in the pre-operative evaluation of renal lesions in the presence of other visceral lesions of equal or more importance. A recent example of this was an elderly man with symptomatic calculous cholecystitis and a mass in the left kidney. An aortogram proved the renal lesion to be a cyst. This procedure has also proved helpful in differentiation between renal parenchymal lesions and other retroperitoneal masses. A normal renal arterial pattern will be found if the kidney is not in-

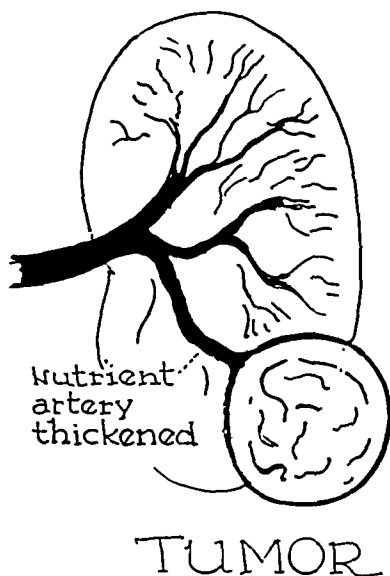


FIG. 2

volved. Aortography will provide accurate differentiation between cysts and tumors of the renal parenchyma. In the case of a cyst there is an obvious avascular area and the vessels are arranged in an "umbrella" pattern (fig. 1) and multiple areas of avascularity will be found in polycystic disease. In tumors there is a thickened nutrient artery, and the area of tumor shows an irregular pooling of the medium in sinusoids (fig. 2). A pitfall is encountered in the case of cystic tumors, where sinusoids are seen at the periphery and the central portion of tumor is relatively avascular. The question of cyst or tumor in this type of case, however, is settled somewhat by the fact that in tumors the periphery of the mass appears thicker, whereas in cysts it is obviously thin.

From an evaluation of the symptoms of renal tumors it seems obvious that they cannot be depended upon to lead to an early diagnosis. From the results that have been reported up to the present time it is apparent that in the majority of cases the tumor has spread beyond the confines of the kidney before any of these symptoms arise. The diagnostic methods now available for recognition of renal tumor are noted for their accuracy and rarely fail if properly applied and

the results correctly interpreted. It appears, therefore, that if a number of asymptomatic lesions are to be diagnosed during a stage when nephrectomy may effect a cure, more routine studies of the urinary tract will have to be done than are currently being done. Rarely does a general physical examination fail to include a roentgenogram of the chest and few pulmonary lesions are encountered which are of more importance than renal tumors. The ease with which excretory urography is carried out and the information gained from it have largely eliminated the objectionable features of studying the urinary tract which formerly existed. As already indicated, it does not within itself suffice to diagnose space-occupying masses of the renal parenchyma but in the presence of good renal function it will indicate variations from the normal that suggest the necessity for other supplementary studies. It is not suggested that routine study of the urinary tract be done on every patient but tumors of the renal parenchyma are found largely in those between the ages of 40 and 55 years and it seems reasonable to suggest that this group be subjected to the same careful consideration of the urinary tract that is given the chest, the gastro-intestinal tract and other systems.

#### SUMMARY

The fact that less than one-third of patients with renal tumors are being cured at the present time indicates the need of providing better methods of diagnosing these tumors in the early stages when cure is more feasible. The triad of symptoms suggestive of renal tumors are hematuria, pain and a mass in the side. However, since these symptoms appear early in less than half the cases, other means of discovering these tumors early enough to effect cures must be employed. Among these are excretory urograms, cystoscopy, retrograde urography and pyelography, perirenal insufflation, exfoliative cytology and aortography. These methods rarely fail if properly performed and accurately interpreted. It would appear that in order to recognize more asymptomatic renal tumors, routine investigation of the urinary tract must be carried out more often than is now being done.

*3503 Prytania St., New Orleans 15, La.*

## RENAL ANGIOGRAPHY

MARVIN HARVARD

*From the Department of Urology, Ochsner Clinic and the Division of Urology, Tulane University School of Medicine, New Orleans*

Visualization of the renal arterial tree by injection of radiopaque medium directly into the aorta was first accomplished in this country about a decade ago by Nelson<sup>1</sup> and Doss and associates.<sup>2</sup> Their early observations opened an entirely new field of urologic investigation. Last year Evans,<sup>3</sup> working with Smith,<sup>4,5</sup> described a simplified apparatus for translumbar injection. Their subsequent reports have been impressive and have served to remove many fears previously associated with direct puncture of the aorta and injection of radiopaque contrast medium. Their most recent report indicates that they have performed over one thousand aortic punctures "without mortality or significant morbidity."

Believing that here was a diagnostic aid whose possibilities should be fully explored, now that the technique had been simplified, we began using it on our service at the New Orleans Charity Hospital in May 1951. It is the purpose of this report to present our experiences during the last 10 months with over 100 translumbar aortic punctures in a wide variety of urologic diseases.

We have adopted the term renal angiography because, like cerebral and cardiac angiography, it would seem to be most appropriate to describe roentgenographic study of the renal arterial tree by injection of contrast media. A theoretically ideal angiogram for urologic diagnostic purposes outlines the entire renal arterial tree and only a segment of the aorta.

### TECHNIQUE

The equipment we use is, with a single exception, the same as that devised by Smith, Rush and Evans.<sup>4,5</sup> We have substituted a polyvinyl plastic tubing as an adapter for their polyethylene tubing. Since the former may be sterilized by autoclaving, the hazards of contamination are somewhat reduced by its use. Similarly, we follow their method of preparing the patient, anesthetization with sodium pentothal and aortic puncture. The medium used is 12 cc of 75 per cent neo-iopax.

### RESULTS

In over 100 translumbar aortic punctures we have had no fatalities, and in most instances only mild transitory discomfort was experienced. The usual

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 3, 1952.

<sup>1</sup> Nelson, O. A.: Arteriography of abdominal organs by aortic injection; a preliminary report. *Surg. Gynec. & Obst.*, 74: 655-662, 1942.

<sup>2</sup> Doss, A. K., Thomas, H. C. and Bond, T. B.: Renal arteriography, its clinical value. *Texas State J. Med.*, 38: 277-280, 1942.

<sup>3</sup> Evans, A. T.: Translumbar arteriography; a preliminary report. *Cincinnati J. Med.*, 52: 47-56, 1951.

<sup>4</sup> Smith, P. G., Rush, T. W. and Evans, A. T.: An evaluation of translumbar arteriography. *J. Urol.*, 65: 911-923, 1951.

<sup>5</sup> Smith, P. G., Rush, T. W. and Evans, Arthur T.: The technic of translumbar arteriography. *J.A.M.A.*, 148: 255-258, 1952.



patient complained of mild discomfort at the site of injection, which lasted no longer than 12 hours. The severest reaction occurred in a woman who weighed less than 100 pounds. Because of her small size and the position of the needle the entire abdominal arterial tree was injected. She experienced abdominal cramps which required mild opiates for 48 hours.

Our most satisfactory angiograms have been made with a 500 milliamperere machine equipped with a high speed Bucky diaphragm, the film being exposed for 0.2 second. The second film, to obtain a nephrogram, is exposed as quickly as the cassettes can be changed. Believing that serial angiography would be more informative, we have attempted to make several angiograms with the high speed rotary cassettes. However, these proved unsatisfactory because of loss of detail in the renal parenchyma. Therefore, we have temporarily abandoned this in favor of the single exposure.

Early in our experience, owing to mechanical failure of a Bucky diaphragm, we discovered that a second puncture with a second injection of medium within a few minutes was tolerated by the patient without noticeable reaction. Consequently, whenever we consider that an injection has been unsatisfactory, the patient is kept anesthetized on the table while the negative is being developed. If the angiogram proves unsatisfactory, a second puncture and injection are made before the patient leaves the table. This has been performed without incident upon several patients, one of whom had hypertension secondary to bilateral nephrosclerosis.

#### CAUSES OF UNSATISFACTORY ANGIOGRAMS

The unsatisfactory angiograms in our series were due to faulty technique in performing the puncture, mechanical failure of the apparatus, or obesity of the patient. Poor placement of the needle in relation to the arterial wall accounted for the greatest number of failures. Either the needle had been moved partially or completely out of the aorta after a satisfactory puncture had been made or the puncture had been incorrectly placed in the beginning. Consequently, the aorta was receiving an inadequate amount of dye, and the dye was being injected either intramurally or extra-aortically. In one of our patients the total quantity of dye was injected intramurally. In 20 minutes it had been partially absorbed and in 1 hour it had completely disappeared.

One inherent difficulty with the translumbar technique is that to be completely efficient it relies upon the branches of the aorta arising from relatively constant positions along its course. The fact that there is a wide variation in the points of origin of these vessels would therefore account for some poor angiograms. Not infrequently, the point of the needle finds its way into the celiac axis, the renal or mesenteric arteries or entirely too low in the aorta. The result is the renals are completely missed or one or the other renal vascular patterns is overemphasized. This type of injection has caused the two severest reactions in our series. Reference has already been made to the first, the young woman whose entire abdominal arterial tree was outlined. The second occurred in a young man who received the entire injection in the right renal artery. Although he complained of

no great pain, the first voiding after injection resulted in hematuria which was evident grossly for 18 hours and microscopically for 36 hours.

The other big source of unsatisfactory angiograms is found in mechanical failure of the apparatus, such as slipping of the adapter, leaking or breaking of the adapter tubing or breaking of the syringe. Similarly, occasionally the roentgen-ray machine may not be operating properly.

Finally, obese patients proved unsatisfactory simply because our needles were not long enough. We had no difficulty in seating the needle in the aorta but a deep breath on the part of the patient quickly pulled the needle out of the aorta.

Anesthetization has not proved a real problem, although the inherent risk of giving a general anesthetic to elderly "poor risk" patients in the prone position must be recognized. Patients are deeply anesthetized for less than five minutes in most cases. The anesthetic is always administered by one skilled in its use and resuscitative equipment is always readily available.

#### INDICATIONS

The published indications for renal angiography are well known. Only those with which we have had experience will be discussed here.

Accurate appraisal of the diseased kidney is essential for intelligent treatment of renal disease. Despite present methods of *renal function* evaluation, frequently it is impossible to determine how much function a diseased kidney actually possesses. In such instances, by demonstrating a good blood supply, angiography may indicate that the kidney can be saved. We have been guided by Doss' dictum that "a kidney is as good as its blood supply". It has changed our procedure on two occasions from nephrectomy to lithotomy and pyeloplasty. Our experience is limited and for purposes of study we have established arbitrary criteria in these cases. If the interlobular vessels are present in at least 50 per cent of their usual number and density and are fairly well distributed, we believe that there is a good chance of preserving the kidney by a conservative surgical procedure. In the presence of bilateral renal disease the angiogram serves the dual purpose not only of estimating the blood supply to each kidney but also of indicating which is more capable of bearing the load alone should it become necessary to sacrifice one.

In differentiation between asymptomatic *cortical tumors* and *cystic disease* our experience has paralleled that of others in that angiography has been found to be a reliable differential diagnostic aid. Asymptomatic tumors which have undergone cystic degeneration may prove difficult to diagnose. The one such case we have encountered revealed characteristic pooling of medium in the very periphery of the lesion and a total lack of vascular markings throughout the remainder. We have used the angiogram to demonstrate a cortical tumor in a young man being studied for hypertension whose only presenting evidence was the slight irregularity of the convexity of the upper pole. There was no pyelographic deformity.

In the study of *renal anomalies* angiography's contributions are obvious. Renal ectopia not otherwise distinguishable from ptosis may be diagnosed by

this means. In surgical procedures on ectopic and other anomalous kidneys knowledge of the vascular pattern is extremely helpful in planning the surgical approach. Proof of renal agenesis may be difficult to obtain at times. By demonstrating the presence or absence of a renal pedicle the angiogram may provide the answer. The presence or absence of an intensified renal shadow in the nephrogram is an additional aid.

*Congenital hypoplasia* and *atrophic pyelonephritis* lend themselves to differentiation by angiography. Each shows considerable decrease in vascularity but the pattern of each is different. The angiogram in uncomplicated congenital hypoplastic kidney is a diminutive of the normal whereas the vessels of the atrophied infected organ are smaller and there is notable lack of cortical arborization.

In general chronic *pyelonephritis* displays characteristic vascular changes. Not only is the caliber of the main renal vessel diminished but the interlobar vessels become narrowed and the interlobular vessels are fewer in number. The cortical arborization has all but disappeared.

In the differential diagnosis of *upper abdominal masses* angiography has also proved helpful. After the possibilities of *pyelography*, *perirenal air insufflation* and intestinal studies have been exhausted, the angiographic pattern may indicate the diagnosis. Both renal and splenic patterns are normally shown by this technique. Not infrequently one is able definitely to state the point of origin of the mass.

In the study of *essential hematuria* by angiography our experience has been equivocal. We have succeeded in solving one particularly perplexing case by definitely establishing a diagnosis of polycystic disease as contrasted to possible tuberculosis. On the other hand, we have not been able to demonstrate small cortical lesions as we had hoped we might nor have we demonstrated any abnormal vascular patterns which may definitely be associated with hematuria.

*Ureteral obstruction* with an apparently nonfunctioning kidney above often presents a dilemma. Whether the kidney may be spared or not depends on many factors. We have found that by demonstrating a good blood supply angiography has served to guide us to the conservative course with happy results. If the renal arterial pattern is almost normal, we unhesitatingly accept it as evidence that the kidney has an excellent chance to recover its function.

Finally, we believe that angiography is indicated in all patients with *hypertension of doubtful etiology*. In the Goldblatt kidney there is definite decrease in the caliber of the vessels to the affected kidney. Perhaps after further study there may emerge other patterns which will be characteristic.

#### SUMMARY

During the last 10 months over 100 translumbar aortic punctures have been performed with no fatalities and in most instances only mild transitory discomfort. Unsatisfactory angiograms were due to faulty technique in performing the puncture, mechanical failure of the apparatus or obesity of the patient. In our experience renal angiography has proved helpful in appraisal of function of the diseased kidney, differentiation between cortical tumors and cystic disease,

renal anomalies, congenital hypoplasia, chronic pyelonephritis, upper abdominal masses, essential hematuria, ureteral obstruction and hypertension of doubtful etiology.

It is hoped that others will adopt the procedure and explore it fully. It is our opinion, after our brief experience, that renal angiography has a definite though limited place in urologic diagnosis and that in time it will become a commonly employed procedure.

*789 Howard Ave., New Haven, Conn.*

## A RUPTURED INTRARENAL ANEURYSM

WILLIAM J. BAKER AND NEIL I. HUCKLEBERRY

Aneurysm of the renal artery, according to the pathological studies of Muller, Bosdorff, Emmerich, Bier and Kment, is relatively rare. It occurs in about 1 per cent of all encountered aneurysms. Any part of the renal artery may be involved: the renal artery, its main divisions, interlobar branches or in the smaller vessels which extend into the parenchyma of the kidney.

Aneurysms of the intrarenal branches of the renal artery are very rare. In the early literature, they were called spontaneous aneurysms. Their rupture usually produces a surgical emergency.

A ruptured intrarenal aneurysm has been encountered by us. The clinical history, physical findings, laboratory data and treatment are very instructive and prompt this report.

### CASE REPORT

I. J., a married Negress, aged 24, was admitted to the Cook County Hospital on July 27, 1949, with the following history: She had delivered twins on May 9, 1949, and had lost 50 pounds during the following 6 weeks. About 2 weeks after the birth of her twins, she had an episode of gross painless hematuria. Her doctor re-admitted her to the hospital and gave her two blood transfusions. The hematuria stopped. No diagnostic work was done. Three weeks later she began a second episode of painless hematuria and after 5 days of bleeding she was admitted to Cook County Hospital. A complete physical and laboratory survey was done, including a retrograde urological survey. The bleeding stopped promptly after pyelography. The patient, anxious to get home to her family, signed a release and was discharged from the hospital. Her history aroused suspicions of tuberculosis but all studies, including a chest film, sputum studies and guinea pig inoculations were negative for an acid fast bacillus. Her bleeding and clotting times were normal. She had moderate secondary anemia. Cysto-ureteroscopy showed bleeding from the left side. Her left ureteropyelogram (fig. 1, A) revealed a compression of the middle calyx and pelvis. It was believed that she had hematuria from a tumor of the left kidney.

She was symptomless for the next 4 months. Her third episode of painless hematuria began on December 15, 1949. It was much more severe. She suffered from dizziness, faintness and spasms of the bladder. She was treated at home for 5 days, after which she was brought to St. Luke's Hospital, in extremis, on December 19, 1949. Her pulse was only 78. The blood pressure was 126 mg. of mercury, systolic and 80, diastolic. The respirations were 18 per minute. So, her condition was actually better than she appeared. There was a large suprapubic tumor and blood was running from the urethra. Her red blood cell count was 2,020,000 and her hemoglobin was 3.9 gm. per cent. An immediate cystoscopy was done. Through an electrotome sheath more than a liter of clots were removed from the bladder. A constant trickle of blood was coming from the left

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 3, 1952.

ureteral orifice. A bilateral ureteropyelogram was attempted. It can be seen (fig. 1, *B*) that the right kidney and ureter are normal. The pyelographic medium did not fill the left pelvis. It was believed that there was a tumor of the left kidney which was causing the bleeding. A blood transfusion was given immediately.

The next morning the patient's condition had grown worse. She was given another pint of blood and sent to the operating room. When the left kidney was exposed there was a pale gray tumor mass in the midportion of the kidney. A nephrectomy was done. The specimen was sectioned immediately by the hospital pathologist and everybody thought we were dealing with a renal neoplasm.

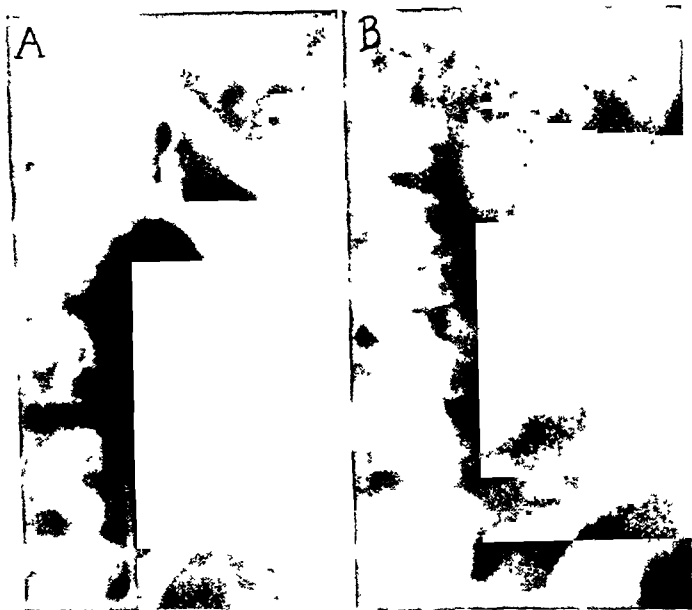


FIG. 1. *A*, Left pyelogram. Compression of middle calyx and renal pelvis. *B*, puddling of medium in left renal region.

Figure 2 shows these cut surfaces. The final pathological diagnosis was "large aneurysm of an intrarenal branch of the renal artery," and the detailed pathological report stated that the left kidney with attached ureter and other structures weighed 221 gm. "The attached ureter is about 20 cm. long and 8 mm. in diameter. The kidney is 12 cm. long, 6.5 cm. wide and in the midportion the thickness is 6 cm. On the anterior surface of the kidney is a bulging nodule that reaches from the convex edge across the center of the kidney toward the hilum 5.5 cm. It is 5.5 cm. long and is elevated above the surface about 3 cm. The external surface is hyperemic, and when this nodule is cut it contains a large amount of brown necrotic material, blood clots and tissues that are tough and elastic, like fibrin. When the kidney is hemisected this mass reaches through and impinges upon the midportion of the pelvis and spreads across into the posterior half. On this surface the largest dimensions of the mass are 3.5 by 3.5 cm. Portions are elastic, fibrillar, grey and brown, and other portions are hemorrhagic. The mass

has a thin fibrous capsule and the material within is grey-brown and dark red laminated fibrin and clotted blood which can be peeled away with moderate resistance, leaving a round sac. The lamination is more marked peripherally and towards the center are soft dark red and red-brown blood clots. A small main artery with a diameter of 3 mm. and 1.5 cm. long extends to the sac structure and divides into three branches. A probe inserted into each extends into the blood clot material within the sac. The cortex of the kidney is brown and has a width of 8 mm. The pyramid tissues are about 16 mm. The capsule strips with slight resistance from a brown surface that is rather smooth except in the region of the nodule. The lining of the renal pelvis and ureter is smooth and glistening. In some of the minor calyces opposite the mass there is a small amount of blood and one of these extends up close to and along the capsule of the mass. In one



FIG. 2. Section of removed kidney. Lesion simulated renal neoplasm.

place there is a break into the sac and blood and blood clot exuding into the calyx. Another minor calyx which is compressed by the mass, has beneath the mucosa red blood clot material. The renal vein is cut off close to the hilum. Its main branches have a smooth lining. A portion from the peripheral edge of the hemorrhagic nodule is fixed for histologic examination.

"The sections of material cut from the edge of the fluctuant mass consist almost entirely of laminae of fibrin mingled with red blood cells and at some levels with leukocytic exudates. At the margin, these tissues merge with a rather well organized fibrous capsule (fig. 3). At a level where the capsule is rather thick and directly continuous with the wall are tissues of an artery with a fibrous tissue thickening of the intima and a muscular hypertrophy of the media tissues. At the margin are other fibrous tissues that extend with compressed renal parenchyma with considerable fibrous stroma, small atrophic tubules and a few glomeruli with vascular but cellular tufts. There are no tumor tissues in the blood clot material. Additional tissues are essentially hyalinized, fibrous, poorly cellular

along the lining edge and moderately cellular at the peripheral margin. There are also some bundles of smooth muscle and focally in the fibrous tissues are small infiltrations of exudate cells, some of them polynuclear leukocytes. There are also masses of fibrin and red blood cells with a few scattered leukocytes. The red blood cells at some levels are in excess. There are no tumor tissues." (The above pathological observations were made by Dr. Edwin F. Hirsch.)

The patient made an uneventful recovery from surgery and was discharged from the hospital after 2 weeks. She has been observed periodically and was last

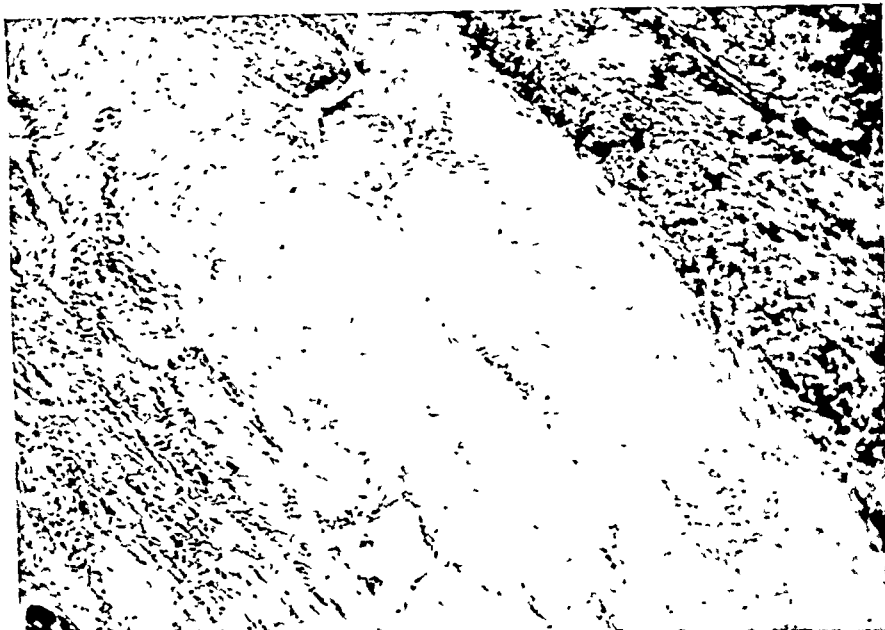


FIG 3 Merging of rather well organized fibrous capsule and tissues of an artery seen on January 16, 1952. Her blood pressure and urine are normal. She feels well and has gained some 30 pounds of weight.

#### DISCUSSION

It is obvious that an intrarenal aneurysm is not easily recognized even when the kidney has been exposed in order to stop painless hematuria which threatens life. Apart from hematuria, these intrarenal aneurysms cause no symptoms or signs that lead to their preoperative diagnosis. One wonders whether pressure nephritis explains the first two episodes of bleeding which our patient experienced.

One cannot classify this aneurysm as traumatic. Over one half of renal artery aneurysms are so classified. A false aneurysm usually follows trauma. Its sac is made of surrounding tissues which wall off the blood. A true aneurysm is one whose sac is formed by the arterial walls one of which, at least, must be intact. From this point of view, our patient's aneurysm must have been a true one. The cause of a spontaneous intrarenal aneurysm would be the same as elsewhere. Atheroma, syphilis, embolism or infection are possible causes. Our patient had no arteriosclerosis or syphilis.



Her hematuria did appear after childbirth, and embolism may have been a factor. She had never complained of a backache. She had never had a palpable tumor in the renal area. This is in striking contrast to traumatic renal aneurysms, the majority of which cause large tumors in the loin and much pain with and without hematuria.

The diagnosis of intrarenal ruptured aneurysm depends chiefly on the marked painless recurrent hematuria and distorted pyelograms. With no history of injury, the presence of a renal neoplasm must be considered. Our patient should have had the benefit of surgical interference 4 months previously. She felt so well after her first pyelography that she elected to go home. Her first pyelogram showed the presence of a compressing intrarenal lesion. An aneurysm was not even considered.

In extrarenal aneurysms of the renal artery, the presence of a wreath-like or signet-ring shadow should make one suspicious of the lesion. Calcified cyst, calcified lymph gland, calcified abscess of the kidney and some types of renal calculus have to be considered in a differential diagnosis.

A nephrectomy affords the best treatment and prognosis, if the other kidney is present and functioning. It is conceivable that small intrarenal aneurysms might be removed. However, the ruptured intrarenal aneurysm is always an emergency and a nephrectomy is probably a lesser surgical insult than attempted conservative procedures.

#### SUMMARY

A ruptured intrarenal aneurysm is reported and discussed.

7 W. Madison Street, Chicago, Ill. (W. J. B.)  
Salt Lake City, Utah (N. I. H.)

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## PERINEPHRIC ABSCESS WITH PERINEPHRO-BRONCHIAL FISTULA: CASE REPORT

LAWRENCE R. WHARTON, JR.

*From the Department of Gynecology, The Johns Hopkins Hospital, Baltimore, Md.*

Perinephric abscess in recent years has become a rather uncommon entity. Parks in 1950, in his study of the radiological diagnosis of this disease, found that perinephric abscesses constituted 0.04 per cent of all admissions to the Johns Hopkins Hospital for the preceding decade or an average of 6.4 admissions per year.

Pulmonary complications, usually pleuritic changes, have been well recognized in association with subdiaphragmatic abscesses, but little attention has been called to similar changes resulting from abscesses developing within Gerota's fascia. The most infrequently found of pulmonary complications have been perinephro-bronchial fistulas. In 1942, Schiappapietra, Felman, and Ghibaudi reported a total of 15 such cases in the literature. Moore and McCarthy added a case in 1944 and Neilson and Dick reported another single case in 1950. The purpose of this paper is to present another such case, bringing the total number of cases to eighteen.

### CASE REPORT

N. McL., J. H. H. 446588, a 34 year old nulliparous Negress, was first seen and admitted to the Johns Hopkins Hospital on March 11, 1952 complaining of pain in the left flank of 2 weeks' duration. For 3 to 4 months, the patient had had dysuria and nocturia. Three months prior to admission, the patient had soreness and aching in her left flank radiating to the left costovertebral angle and downward to her left groin. She then had a high fever with chills. She consulted an "herb doctor" who gave her pills and herbs, and in about one week the patient improved. A month later, the patient had a similar attack with flank pain, chills, and fever and was again given pills with partial relief of symptoms.

A third similar attack occurred 2 weeks before admission, again characterized by chills, hyperpyrexia, dysuria, urgency, and frequency of urination. There had been no history of hematuria or passage of stones. At about the same time the patient noted a slight nonproductive cough. The past, family, and social history was otherwise irrelevant except for a long history of chronic alcoholism.

On admission, the patient appeared to be acutely ill with minimal distress. Her temperature was 103F, pulse 136, respirations 26. The lungs were described as clear. The liver was enlarged and was palpable three finger breadths below the right costal margin. In the left flank there was a tender, poorly defined mass which did not move with respirations. The remaining physical examination was unrevealing.

Laboratory studies revealed an anemia with a hemoglobin of 8.6 gm. and white count of 23,000. The catheterized urine was acid, specific gravity 1.010, no sugar, 1 plus albumin, and forty to fifty white cells per high power field. The phenolsulfonphthalein excretion was 63 per cent in 2 hours.

The patient was placed on sulfadiazene while awaiting culture reports. Fluid intake was adequate but was supplemented by intravenous fluids. The nonprotein nitrogen was 20 mg. per cent, blood sugar 117 mg. per cent. There was evidence of liver damage which was believed to be due to an alcoholic cirrhosis. X-ray of the chest on March 12, 1952 revealed a large left pleural effusion with a suggestion of underlying parenchymal changes in the left lower lobe (fig. 1, A). X-ray of the abdomen showed an area of increased density and calculi in the left upper quadrant. Transfusions of whole blood were given with no effect on the anemia. Leukocytosis and pyrexia persisted. Penicillin was added to the sulfadiazene.

On March 13, the patient became dyspneic and a more severe cough developed, productive for the first time of a foul-smelling, bloody sputum. Physical findings now confirmed consolidation and effusion of the left lower lobe of the lung. A



FIG. 1. A, preoperative chest x-ray following thoracentesis; note parenchymal infiltration and pleural effusion. B, postoperative x-ray showing left staghorn calculus. C, postoperative left retrograde pyelogram; calculus fills upper calyces; calycectasis.

thoracentesis yielded a small amount of thick, sanguino-purulent fluid. At that time, it was thought that the patient had a perinephric abscess with a pleural reaction. Sputum cultures showed pneumococci, *Neisseria*, and alpha and gamma streptococci. No acid fast organisms were found. Urine culture showed coli aerogenes.

With the hemoptysis which continued the temperature fell to normal. Chloromycetin was then started and other antibiotics discontinued since sensitivity studies showed the coli aerogenes to be most sensitive to this drug. A repeat thoracentesis was done on March 14 with the same results as before.

Cystoscopy on March 14, 1952 revealed marked subacute cystitis. Left ureteral catheterization was done, but the catheter would pass only about 3 cm. up the left ureter. No urine drained through the catheter. A repeat chest x-ray on March 14 showed left lower lobe pneumonitis and there was a suggestion of a left sub-diaphragmatic abscess. The x-rays were unchanged on March 15. A barium enema

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study on March 15 showed downward displacement of the transverse colon and splenic flexure. The staghorn calculus was present on the left, and a dextroscoliosis of the lumbar spine was present. A gastro-intestinal series showed a large mass displacing the stomach anteriorly and laterally. There was no visualization of the left kidney on excretory urography; the right kidney was normal.

During March 14-15 the hemoptysis ceased and the temperature climbed from 98.6F to 104F. Leukocytosis and anemia persisted despite more transfusions. It was believed that the patient had a perinephric abscess with an empyema involving the left lower lobe of the lung and the patient was taken to the operating room on March 16, 1952.

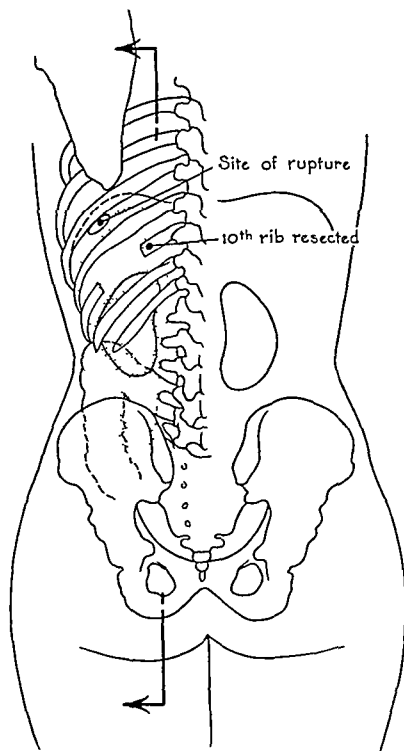


FIG. 2. Schematic reconstruction, posterior view, of perinephric abscess.

A left lumbar incision was first made parallel to the twelfth rib. On entering Gerota's fascia there was the release of about two to three quarts of bloody, foul-smelling pus. The left kidney could then be palpated. It was somewhat larger than normal and displaced anteriorly almost against the rib cage. The calculus could not be felt. When the perinephric abscess was evacuated as completely as possible, a left thoracotomy was done by Dr. A. Glenn Morrow, resident in surgery, by resecting a portion of the tenth rib (fig. 2). Extrapleural open drainage of a large lung abscess was then accomplished. By exploring through the perinephric and lung abscess cavities simultaneously, a two to three centimeter defect was found in the posterior leaf of the diaphragm at the junction of the

psoas muscle, joining the perinephric and lung abscesses. Open drainage of the lung abscess and perinephric abscesses was done packing the abscess with iodoform gauze. A 32F catheter was passed down the perinephric abscess to about the level of the crest of the ileum. A large rubber tube was placed to extend up to the defect in the diaphragm. The kidney was not removed because of a mild degree of shock during the procedure and because of the anemia.

The patient did extremely well. The maximum temperature on March 17 was 100.4F; thereafter, the temperature was essentially normal. The patient received penicillin and terramycin simultaneously. Without further transfusions, the anemia disappeared, as did the leukocytosis. Marked pyuria continued. Cultures from the lung abscess, perinephric abscess, and urine yielded coli aerogenes. The lung cleared gradually with only pleural thickening remaining at the left base. All drains were finally removed on April 2, the eighteenth postoperative day. The wounds were allowed to granulate and close slowly. The patient was discharged on April 11, 1952, her twenty-seventh postoperative day. Postoperative x-ray and retrograde pyelograms are shown in figure 1, *B* and *C*.

The patient was followed closely and both incisions had filled in and were closed on May 16, 1952. The pyuria has persisted and coli aerogenes has remained as the offending organism.

Cystoscopy was repeated on April 29, 1952. This time the left ureter was catheterized with ease. The left kidney had a 10 per cent excretion of phenolsulfonphthalein in 30 minutes, and the right 25 per cent in the same time. The left retrograde pyelogram showed incomplete filling, but the staghorn calculus was seen to be present in the region of the left superior calyces.

The final diagnoses were: Nephrolithiasis, left; perinephric abscess, left, due to coli aerogenes with rupture through left diaphragm into lung; lung abscess, left due to coli aerogenes; perinephro-bronchial fistula; probable cirrhosis, liver.

#### DISCUSSION

This case was of interest in that, with spontaneous partial drainage of the abscesses through the bronchial tree, there was a temporary recession of the fever to normal. Complete and thorough drainage of the perinephric and lung abscesses resulted in a dramatic response on the part of the patient demonstrating that, despite all the antibiotics, there still is no substitute for surgical drainage. Moreover, we believe that drainage of the perinephric abscess alone would not have constituted adequate drainage of the lung abscess despite the transdiaphragmatic communication.

Perinephric abscesses have been classified into primary and secondary types. The primary group, metastatic or extrarenal in origin, is the result of blood-borne infections or trauma. The secondary or non-metastatic group is the result of direct extension of the inflammatory reaction from the kidney following pyelonephritis, cortical abscess, carbuncle, lithiasis, tuberculosis, rupture of the kidney, or ureteral disease. Also, abscesses as a result of direct extension from the adrenal or gastro-intestinal tract are included in this category. The staghorn calculus present in this case was without doubt the exciting factor.



The mechanism of extension of the inflammation from the renal parenchyma to the perinephrium has been a matter of some controversy. It seems probable that the dissemination is through the end arteries in the kidney cortex to the perinephrium by branches of these cortical arteries communicating through the capsule to the perinephrium. Also, lymphatic communication and direct extension such as rupture of a cortical abscess are other modes of transmission.

Gerota's fascia which encompasses the perinephrium has been likened to an inverted, pear-shaped sac. Its anterior and posterior sheaths fuse laterally to the transversalis fascia and, medially these sheaths cross the midline anterior to the great vessels. Superiorly, the sheaths fuse with the fascia of the psoas and quadratus lumborum muscles and fuse with the subdiaphragmatic fascia. This region forms a fairly strong point, which accounts for the paucity of cases of rupture through the diaphragm. The weakest point in this region seems to be the point where the psoas fibers pass beneath the arcuate ligament of the diaphragm to insert in the sides of the transverse process of the twelfth thoracic vertebra. In this particular case, it appears that the pus followed this route. The weakest point in Gerota's fascia is in the inferior aspect as it extends downward from the kidney to surround the ureter and spermatic or ovarian vessels. It is not unusual for perinephric abscesses to follow this course, as was true in this case also. Occasionally, these abscesses will point to the groin as a psoas abscess.

This particular case demonstrated many of the diagnostic radiological findings: A mass was present in the left upper quadrant; the kidney and psoas outlines were obliterated; there was lumbar scoliosis with the convexity away from the abscess; and there was displacement of the stomach, transverse colon, and splenic flexure. The diaphragm was fixed. The kidney was not visualized to demonstrate its fixation. Only the calculus was seen.

Surgical drainage is the accepted method of treating such abscesses and perhaps was delayed too long in this case while the various studies were being made. The lapse in time, however, did demonstrate that the antibiotics were ineffectual in controlling the abscess without drainage since penicillin, sulfadiazine, and chloromycetin were used preoperatively. *Coli aerogenes* was found in the urine, perinephric abscess, and lung abscess. This organism has persisted in the urine despite antibiotics postoperatively.

The problem of nephrectomy at the time of drainage of perinephric abscesses is one which must be decided with each case. Many times nephrectomy will not be indicated particularly in the primary group. When the abscess is small and an indication for nephrectomy exists, nephrectomy may be done provided the patient is in good general condition. In this particular case, kidney surgery was and is indicated in the presence of a staghorn calculus, impaired renal function, and a persistent urinary tract infection despite antibiotics. At the time of drainage of the abscesses, the patient's general condition was too precarious to risk further surgery and nephrectomy was not done. We are, however, considering nephrectomy at a later date when the patient has completely recovered from her ordeal.

## SUMMARY

A case of perinephric abscess with extension through the diaphragm to form a lung abscess with resulting perinephro-bronchial fistula is presented. The cause of the perinephric abscess was a staghorn calculus and pyelonephritis due to coli aerogenes.

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## PERI-URETEROPELVIC CYST

JACK HYMAN

The ensuing case presentation records an unusual pathologic entity which was not only unsuspected preoperatively but once discovered could not be named for want of previous description. A search of available literature has failed to disclose a similar case though I am reasonably sure that it must have occurred in the past.

### CASE REPORT

A 58 year old white woman (Mrs. L. H.) had been well until the early hours of the morning September 4, 1949, when she was awakened by severe pain in the upper right abdomen. The pain was constant, throbbing, and penetrating into the back. Nausea accompanied the pain. She was seen shortly after the onset by one of her sons, a physician. The temperature, blood pressure and pulse were found to be normal. An opiate and atropine were administered with only slight relief of pain. The patient was admitted to the hospital later in the morning.

There was no previous history of similar episodes of pain. The past urologic history was entirely devoid of significant events except for mild frequency and nocturia of two to three times for several years. Past general health had been excellent. The only previous surgery was the removal of a cervical polyp many years ago. Two normal pregnancies and deliveries were without urologic complication.

Upon admission to the hospital the patient was examined by a general surgeon who found a small slender female apparently acutely ill and having considerable abdominal distress. The temperature, pulse, respirations and blood pressure were within normal limits. Abnormal physical findings were limited to the abdomen. The abdomen was flat, symmetrical and generally tense. There was slight tenderness over the whole right side, a little more marked in the upper quadrant. A questionable mass was vaguely palpated in the right upper quadrant. Peristaltic sounds were present, but diminished in rate and intensity.

The laboratory reported a mild leukocytosis with a slight shift to the left. The urine was reported as negative except for 3 to 5 white blood cells per high power field in an uncentrifuged voided specimen. Supine and erect roentgenograms of the abdomen showed no abnormality. A roentgenogram of the chest was not abnormal. Excretory urograms (fig. 1) were done the day after admission. There was prompt excretion of contrast material from both kidneys. Filling was incomplete and even after 75 minutes the ureters failed to visualize. In retrospect one might suggest that there was upward and lateral displacement of the right kidney to a minor degree.

Our initial contact with the case was in being asked to review the pyelograms. It was believed that a bilateral upper urinary tract abnormality was present, a little more marked on the right, but that the roentgenograms were not thoroughly diagnostic and retrograde studies would perhaps clarify the situation. The pati-

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 4, 1952.

ent's physician sons were very reluctant to disturb their mother by this procedure and the presence of severe unilateral pain with bilateral roentgen findings made it seem probable that the pain was not from the urinary tract, so we did not strongly urge the study.

During the morning abdominal pain continued with the same intensity in spite of regularly administered opiates and surgical exploration was decided upon.

The abdomen was explored by Dr. Warren A. Yemm. A right transrectus incision was utilized. The only abnormality that was found was a mass in the right renal area. The author was called and asked to expose the right kidney. Our initial contact with the patient was at the operating table.

Additional exposure was obtained by lateral transverse extension of the upper limb of the incision. The peritoneum was incised along the lateral margin of the ascending colon almost to the hepatic flexure. The ascending colon was retracted

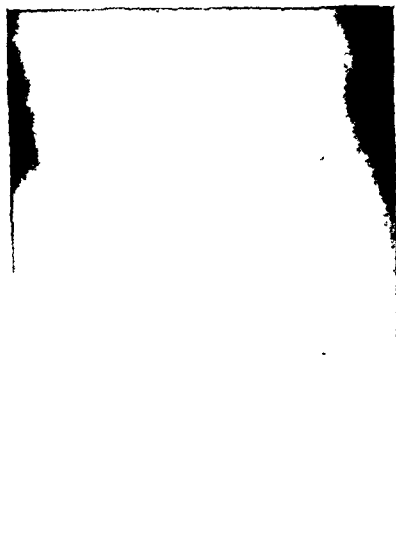


FIG. 1. Preoperative urogram

medially exposing the kidney enveloped in the perirenal fascia. The fascia was incised over the anteromedial aspect of the kidney and bluntly dissected off the surface of the kidney and what appeared to be a large distended extrarenal hydronephrotic pelvis. There was extensive edema of the peripelvic and perirenal fat and fascia. The apparent hydronephrotic pelvis was fusiform in shape and seemed to terminate by junction with an upper ureter of normal caliber. There was no extrapelvic lesion at the ureteropelvic junction to account for obstruction; nor had this finding been suggested by the original pyelograms. What appeared to be the pelvis and the upper ureter were completely mobilized along with the lower two thirds of the kidney. Exploration of the renal pelvis was intended and a longitudinal incision was made on its anterior surface which released under pressure about 150 cc of clear, nonodorous fluid. We were amazed to see the ureter slightly reduced in caliber coursing within this cyst-like cavity (fig. 2). The incision was

extended inferiorly to the junction of the cyst wall with the upper ureter and superiorly to the hilum of the kidney. The intracystic ureter was loosely adherent to the medial wall of the cystic cavity and joined a small intrarenal pelvis at the hilum. Approximately 8 cm. of ureter was within the cystic cavity and two small blood vessels passed from the cyst wall to the ureter about 2 cm. from the ureteropelvic junction. The ureteropelvic junction appeared to be normal. About 3 cm. from the ureteropelvic junction, there was a narrowed segment of ureter whose caliber was about one half the caliber of the remaining ureter for a distance of about 1 cm. Thin strands of fibrinous material were present at the angles where the cyst was in continuity with the lower segment of the ureter and where it

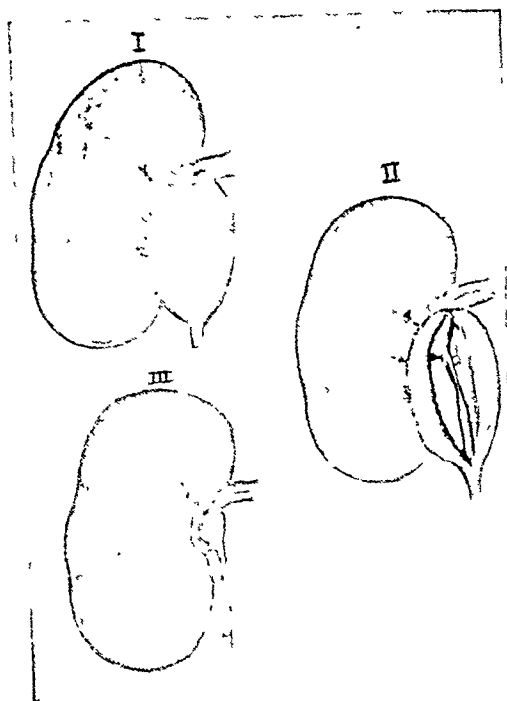


FIG. 2. Diagrammatic sketch of condition found at operation

surrounded the pelvis at the hilum. The cyst wall was completely resected by severing it from the ureter below and from around the pelvis at the kidney. No communication could be found between the cystic cavity and the renal pelvis or ureter. The two small vessels attached to the upper ureter were ligated. A stab wound was made in the right flank to allow the egress of a rubber tissue drain. The perirenal fascia and peritoneum were approximated. The left kidney was carefully palpated before closure and no gross abnormality could be detected.

The patient's immediate postoperative condition was excellent. When she had fully recovered from the effects of the anesthetic, it was apparent that the severe pain was no longer present and did not recur thereafter. For 3 days after surgery there was profuse, serous, nonodorous drainage from the stab wound drain in the

flank. The drainage lacked the chylous character of lymph and was definitely not urine. This drain was removed on the fourth postoperative day and the wound healed promptly. Except for the occurrence of post-catheterization cystitis, the remainder of the convalescence was without incident. The patient left the hospital on the fourteenth postoperative day. Two and a half years have elapsed since surgery and she has remained well.

About 9 months after operation, after persistent urging, an excretory urogram was made (fig. 3). The left upper urinary tract was unchanged and still showed a bizarre calyectasis. The left ureter again did not visualize. It must be assumed that a mild ureteral stricture is present on the left similar to that found at surgery in the upper right ureter. The right kidney was much better delineated than in the preoperative films. The calyectasis was reduced. The ureteropelvic junction



FIG. 3. Postoperative urogram

was visualized and about two thirds of the distal ureter. One can conclude that drainage was improved by resection of the cyst.

#### ETIOLOGY

The probable etiology of this unique peripelvic and peri-ureteral cyst formation prompts the ensuing remarks.

Microscopic sections of the cyst wall provided the best clues to the nature of the cyst. Hemotoxylin and eosin stains revealed the wall to be principally fibrous tissue with a moderate amount of fat. No epithelial or endothelial lining could be identified. Sections sent to the Armed Forces Institute of Pathology were stained by the elastic tissue and Van Giesen stains and showed elastic and degenerating smooth muscle fibers.

Dr. F. K. Mostofi<sup>1</sup> of the Institute suggested that the cyst might be an

<sup>1</sup>Mostofi, F. K.: Personal communication

extended inferiorly to the junction of the cyst wall with the upper ureter and superiorly to the hilum of the kidney. The intracystic ureter was loosely adherent to the medial wall of the cystic cavity and joined a small intrarenal pelvis at the hilum. Approximately 8 cm. of ureter was within the cystic cavity and two small blood vessels passed from the cyst wall to the ureter about 2 cm. from the ureteropelvic junction. The ureteropelvic junction appeared to be normal. About 3 cm. from the ureteropelvic junction, there was a narrowed segment of ureter whose caliber was about one half the caliber of the remaining ureter for a distance of about 1 cm. Thin strands of fibrinous material were present at the angles where the cyst was in continuity with the lower segment of the ureter and where it

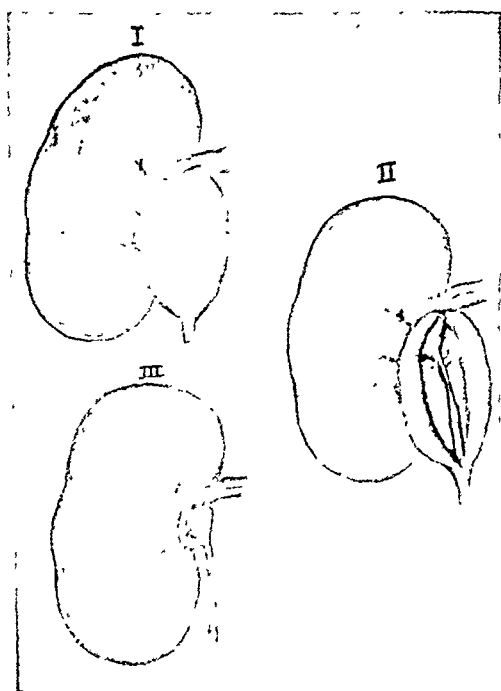


FIG. 2. Diagrammatic sketch of condition found at operation

surrounded the pelvis at the hilum. The cyst wall was completely resected by severing it from the ureter below and from around the pelvis at the kidney. No communication could be found between the cystic cavity and the renal pelvis or ureter. The two small vessels attached to the upper ureter were ligated. A stab wound was made in the right flank to allow the egress of a rubber tissue drain. The perirenal fascia and peritoneum were approximated. The left kidney was carefully palpated before closure and no gross abnormality could be detected.

The patient's immediate postoperative condition was excellent. When she had fully recovered from the effects of the anesthetic, it was apparent that the severe pain was no longer present and did not recur thereafter. For 3 days after surgery there was profuse, serous, nonodororous drainage from the stab wound drain in the

flank. The drainage lacked the chylous character of lymph and was definitely not urine. This drain was removed on the fourth postoperative day and the wound healed promptly. Except for the occurrence of post-catheterization cystitis, the remainder of the convalescence was without incident. The patient left the hospital on the fourteenth postoperative day. Two and a half years have elapsed since surgery and she has remained well.

About 9 months after operation, after persistent urging, an excretory urogram was made (fig. 3). The left upper urinary tract was unchanged and still showed a bizarre calyectasis. The left ureter again did not visualize. It must be assumed that a mild ureteral stricture is present on the left similar to that found at surgery in the upper right ureter. The right kidney was much better delineated than in the preoperative films. The calyectasis was reduced. The ureteropelvic junction



FIG. 3. Postoperative urogram

was visualized and about two thirds of the distal ureter. One can conclude that drainage was improved by resection of the cyst.

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aneurysmal dissection of the ureteral wall whereby the outer layers of the ureter had been separated from the inner. He notes that the absence of an endothelial lining, the fact that the cyst formed a sheath around the ureter with which it was connected by two tiny blood vessels and merged with the ureter and pelvis at either end, along with the close resemblance of the cyst wall to the outer layer of the ureter all support this probability.

Dr. Mostofi postulated the following possible history. "It is possible that sometime in the past a small transient blow-out of the ureter may have occurred with extravasation of a small amount of urine into this area, resulting in a serous exudation either before or after the acute phase and terminating in the formation of this cystic structure. If so the rupture must be assumed to have been incomplete, going through only part of the wall and not reaching the outer fibromuscular and adventitial layers."

Dr. A. J. Scholl<sup>2, 3</sup> published an excellent review of peripelvic lymphatic cysts recently, which prompted consultation with him for his opinion. He very kindly wrote us that he had never seen or heard of a case like this and supported Dr. Mostofi's suggestion.

It is very difficult to reconcile such a cyst formation as a congenital lesion since our concept of the embryologic development of the urinary tract would not construe a malformation of this type. We must accept the most logical theory as that of an aneurysmal-like dissection of the ureteral or pelvic wall. The patient's past history is devoid of incident which might suggest the onset of this process but it must have started sometime and somehow.

#### DISCUSSION

One might conjecture about the means of making a preoperative diagnosis in this or a similar case if it should occur. The outstanding symptom would be severe unremitting upper right abdominal pain accompanied by nausea; the source of which necessarily would be difficult to find by virtue of the absence of other clinical signs.

Clinical laboratory findings would likewise fail to be informative. Careful, complete roentgen studies might strongly suggest the diagnosis if the possibility were kept in mind. Mild calyectasis without apparent intrinsic obstruction would probably be present. Even though a ureteral stricture was demonstrated at surgery in this case, it was evident from the postoperative pyelograms that it was not solely responsible for the dilatation.

Retrograde pyelography with oblique and lateral projections would very likely demonstrate displacement of the upper third of the ureter medially and anteriorly. The lower pole of the kidney itself would probably be displaced laterally and superiorly. The most diagnostic finding would be effected by perirenal air study concomitant with pyelography which could demonstrate a peri-ureteral mass in continuity with the renal shadow through which the ureter would seem to be coursing.

<sup>2</sup> Scholl, A. J.: Peripelvic lymphatic cysts of the kidney, *J.A.M.A.*, **136**: 4-7, 1948.

<sup>3</sup> Scholl, A. J.: Personal communication

After this seemingly learned discussion, the author must admit that if and when he encounters a similar case, the diagnosis will again, if made at all, be very likely made at surgery.

#### SUMMARY

An extremely unusual case of peri-ureteral and peripelvic cyst formation has been presented.

The clinical syndrome, operative findings, and surgical management have been described.

The probable etiology based on the gross and microscopic pathology has been suggested to be an aneurysmal dissection of the ureteral wall with subsequent cyst formation.

Methods of making a preoperative diagnosis of such a lesion in the future have been suggested.

*1302 Government St., Mobile, Ala.*

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On pathological studies, the specimen consisted of an enlarged right kidney and a short portion of the proximal ureter. The pelvis of the kidney was obviously hydronephrotic. The muscular wall of the ureter was found to be lying within an



FIG. 1. Case 1. Retrograde pyelogram showing moderate hydronephrosis with failure of filling of ureter.

envelope of firm plastic tissue (fig. 2). It was significant (fig. 2) that this peri-ureteral tissue was grossly distinct from the muscular wall of the ureter to which it was adherent. Microscopic examination of the thickened peri-ureteral adventitia (fig. 3) revealed evidence of subacute and chronic peri-ureteral inflammation. Eosinophils were moderately numerous and a few polymorphonuclear leukocytes were scattered throughout this altered peri-ureteral fatty tissue. A number of perivascular lymphoid collections were seen. Van Gieson stains showed a sparse formation of new connective tissue fibrils. Bacterial stain of the tissues revealed some gram positive cocci. The renal cortex indicated some pyelonephritic changes, but from the appearance of the glomeruli and tubules, the kidney could have been salvaged had the obstruction been properly relieved.

*Case 2.* Mrs. J. W. H., Univ. of Va. Hosp., a 46 year old woman, gave a past history of excellent past health without genito-urinary symptoms. Three days

## PERI-URETERITIS PLASTICA: A REPORT OF FOUR CASES

SAMUEL A. VEST AND BRUNO BARELARE, JR.

*From the Department of Urology, University of Virginia Hospital, Charlottesville, Va.*

The clinical condition which we wish to report here must be relatively rare. According to a perusal of the literature, similar instances have not been described although such cases must have been encountered previously by urologists. However, we have now encountered 4 cases which we believe are the result of a single disease process. For this reason, we have called this condition peri-ureteritis plastica. We selected this designation because the disease reminded us of the so-called linitis plastica of the stomach in which the plastica denotes that the wall of the stomach has become thickened and plastic-like in nature. Perhaps, a better term for the condition reported here would have been "chronic peri-ureteral lymphangitis." We are making this report with the hope that in the future others with similar cases may apply proper corrective surgery without sacrifice of renal substance.

A number of retroperitoneal and intraperitoneal diseases have been known in the past to have produced obstruction to the ureters resulting in hydronephrosis with frequent associated loss of vital kidney function. Ormond, Ewell, and Amselem each have recently reported interesting cases in which the ureters were obstructed by peculiar retroperitoneal masses. The following cases reported here, we believe, are unique and not similar to those of the above authors. The clinical findings in the first case led us to suspect the possibility of hydronephrosis occurring secondary to plastic or hypertrophic changes in the peri-ureteral tissues. Our cases will be reported in brief.

### CASE REPORTS

*Case 1.* C. C., Univ. of Va. Hosp. No. 74248, a 48 year old white man, gave a history of gonorrheal cystitis several years prior to having a transurethral resection for a median bar obstruction. Following the latter there was an intense persistence of urinary symptoms consisting of urgency, frequency, and painful urination. Studies at this time revealed gram positive cocci in the bladder urine but cultures from the right kidney were sterile. Retrograde pyelograms revealed both upper urinary tract systems to be within the limits of normal. Because of persistent urinary symptoms unrelieved by sulfanilamide medication, a perineal prostatectomy was performed approximately a year later at a neighboring hospital. His bladder symptoms entirely disappeared after the prostatectomy. The patient was well for 2 years but for a year prior to his next admission, he noticed the onset of right flank pain which at times was severe. There were no chills, fever, or lithuria. Urine was entirely negative on microscopic. A plain urogram showed no evidence of calculi in the urinary tract but retrograde pyelograms (fig. 1) demonstrated a so-called grade 2 hydronephrosis of the right kidney. The left kidney was normal. The right ureter did not fill with contrast medium and it was

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 6, 1952.

assumed that the obstruction was at the site of the ureteropelvic junction. Cystoscopic dilatation of the right ureter over the next few months did not alleviate the episodes of right flank pain. Accordingly, exploration of the right kidney and ureter was carried out. Exposure through the right flank incision revealed the perirenal fat to be adherent to the renal capsule. The ureter emerging from the kidney was remarkable in that it was involved in a circular mass approximately 3 cm. in diameter. The mass was firm and adherent to the lumbar muscles. This large ureteral mass was dissected free and developed down towards the pelvic region. The entire mass was divided and ligated, following which the kidney was removed. The patient made an uneventful recovery and has remained well.

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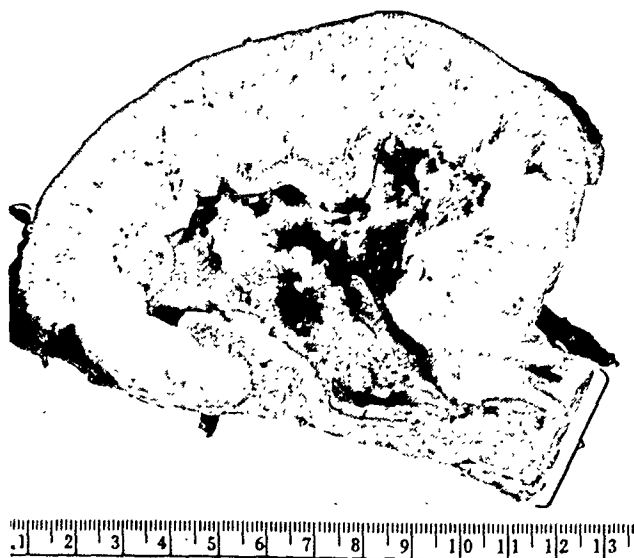


FIG. 2. Case 1. Bisected of moderately hydronephrotic kidney after removal. Note overall diameter of large ureter and distinct division between ureter proper and hypertrophied peri-ureteral tissue.

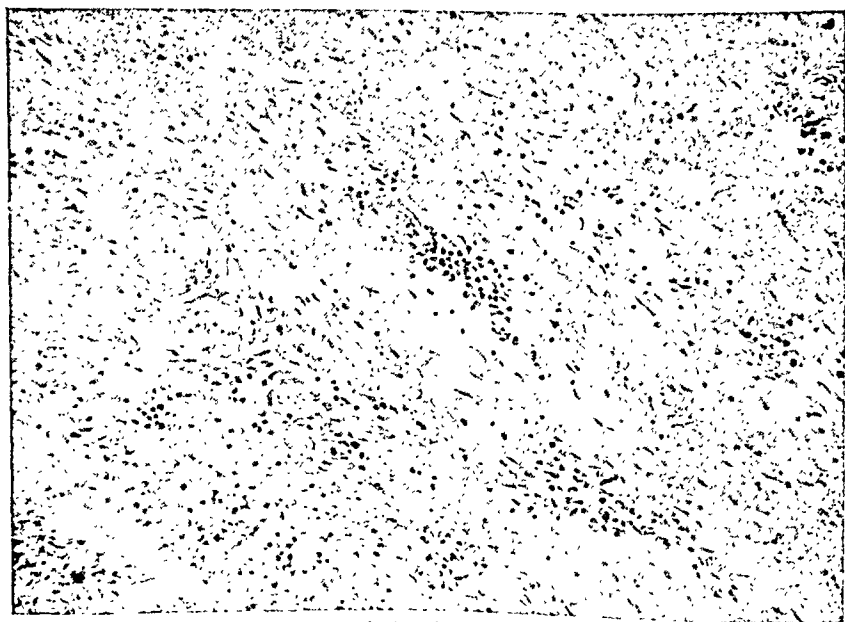


FIG. 3. Case 1. Section is characteristic of thick plastic envelope surrounding ureter. It shows modified or altered fat cells, few fibrils of fibrous tissue, few polymorphonuclear leukocytes, eosinophils, and some lymphoid collections.

prior to admission while working she was suddenly seized with severe pain in the right flank which radiated to the right groin and buttock. The flank pain was constant and accompanied by low grade fever of 100F. No chemotherapy of any

type had been administered. She was admitted in moderate distress with tenderness on deep palpation in the region of the right kidney. Catheterized urine showed numerous white blood cells and occasional red blood cells, but cultures from the bladder and both kidneys were sterile. Cystoscopic examination revealed the presence of edema of the right ureteral orifice. Indigo carmine injected intravenously showed good concentration from the left ureteral orifice in 3 minutes with no dye from the right ureteral orifice in 10 minutes of observation. A No. 5 ureteral catheter was then passed to the right kidney without meeting any obstruction following which there was an immediate flow of faintly blue colored urine. The right ureter did not fill with contrast medium.

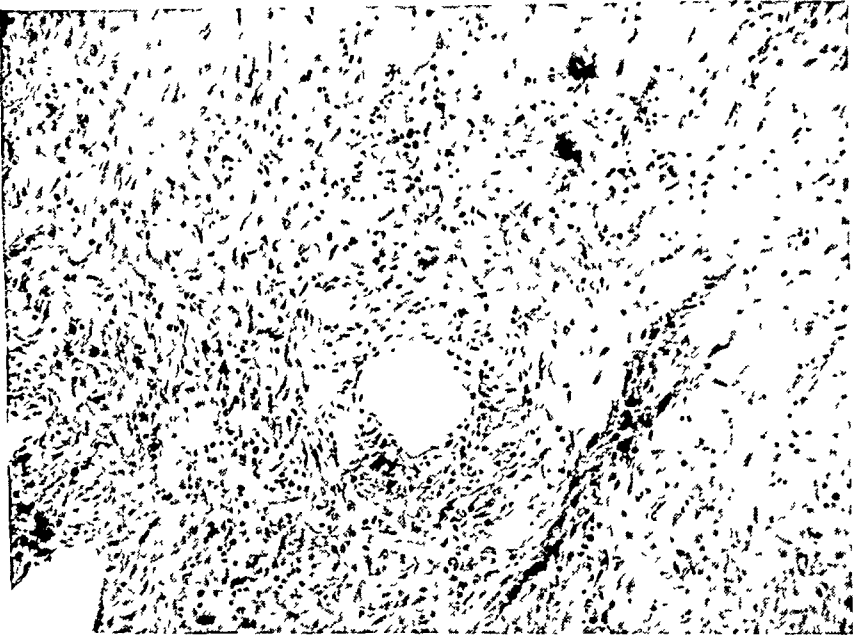


FIG. 4. Case 2 Peri-ureteral plastic tissues showing the altered fat containing scattered polymorphonuclear leukocytes and round cells indicating chronic and subacute peri-ureteritis.

The next day exploration was performed for the unexplained acute obstruction to the right kidney. On dividing the lumbodorsal fascia a fibrous tissue mass was encountered which seemed to surround the kidney. On further exploration the ureter was found to be enveloped by a thick capsule identical to that described in case 1. Obstruction of the kidney resulted from compression of the ureter by this distinct peri-ureteral envelope. Because of the possibility of recurrence by further fibrous changes with subsequent obstruction to the kidney, the operator decided, as in the first case, on nephrectomy. The kidney was removed following which convalescence was uneventful. Postoperative follow-up of the patient has revealed no urinary symptoms with normal findings on examination of the urine.

A photograph of the remarkably enlarged ureteral mass was unfortunately not obtained but pathological study of the peri-ureteral tissue (fig. 4) revealed subacute and chronic inflammation in the altered peri-ureteral fat similar to that in



the first case. Van Gieson stain showed some new fibrils of fibrous tissue to be sparsely present. Bacteriological stains of the peri-ureteral and peripelvic tissue did not reveal any organisms to be present. Microscopic examination of the renal cortex showed a few areas of round cell infiltration indicating minimal infection of the renal parenchyma. In retrospect, it was apparent that the kidney could easily have been saved had the obstruction factor been relieved.

With such experiences in mind, we have since been on the alert for similar cases in which we might prevent progressive renal destruction by relieving the obstructive factor resulting from plastic peri-ureteral inflammatory changes. The following is a case in point.

*Case 3.* F. R., Univ. of Va. Hosp. No. 138294, a 46 year old white man, was first seen complaining of gross hematuria. Urological examination revealed that he had a grade 2 papillary epidermoid carcinoma of the bladder associated with evidences of cystitis. Excretory urograms were normal. Renal function was normal on both sides but cultures from the bladder and right kidney revealed a non-hemolytic streptococcus infection for which he received sulfanilamide medication. The bladder tumor was treated and thought to be destroyed by fulguration but the patient was re-admitted 3 years later with a recurrence of the bladder neoplasm. Thorough fulguration of the tumor was carried out this time through a suprapubic cystotomy. Cultures of the bladder urine at that time revealed *B. coli* organisms present and the patient received sulfathiazole medication. Subsequent cystoscopies during the next 18 months revealed no further recurrence of the bladder neoplasm.

The patient then began to note the onset of frequency of urination, mild suprapubic discomfort, and episodes of fever. These symptoms were subsequently controlled by the administration of sulfa drugs. Cystoscopy revealed chronic cystitis to be present at the base of the bladder in the previously fulgurated area and biopsy showed no evidence of tumor. A catheter was inserted to the left renal pelvis with ease but some obstruction was encountered in the lower right ureter. Purulent urine was obtained from the right kidney through the ureteral catheter and a pyelogram (fig. 5) revealed obvious hydronephrosis with the opaque material failing to fill the right ureter. A plain urogram showed no evidence of urinary tract calculi and the tentative impression was that the ureter probably contained soft non-opaque calcareous material.

Operation: Through a modified McBurney incision, the peritoneum was reflected medially and the ureter exposed. The ureter (fig. 6) was remarkably thickened, approximately 4 cm. in diameter, and indurated to palpation. Recalling our previous experience, we opened the plastic peri-ureteral tissue and found the inlying ureter to be well differentiated from the encompassing sheath or envelope. The muscular wall of the ureter was only slightly thickened. A ureterotomy opening was then made in the mid-ureter through which a No. 14 rubber catheter was easily inserted to the bladder and also to the kidney pelvis without encountering any obstruction in either direction. There was a profuse drainage of purulent appearing urine from the kidney pelvis. When no intra-ureteral obstruction was encountered, it was decided to completely remove the

plastic envelope, thus relieving the peri-ureteral compression. A longitudinal incision was made through this tissue (fig. 7) down to the region of the base of the bladder and up to the renal pelvis, thus easily freeing the ureter. The No. 14 urethral catheter was then re-inserted through the ureterotomy to the renal



FIG 5 Case 3 Hydronephrosis of right kidney following removal of catheter after retrograde pyelogram. Note that middle and lower ureter failed to fill beginning at point just below kidney

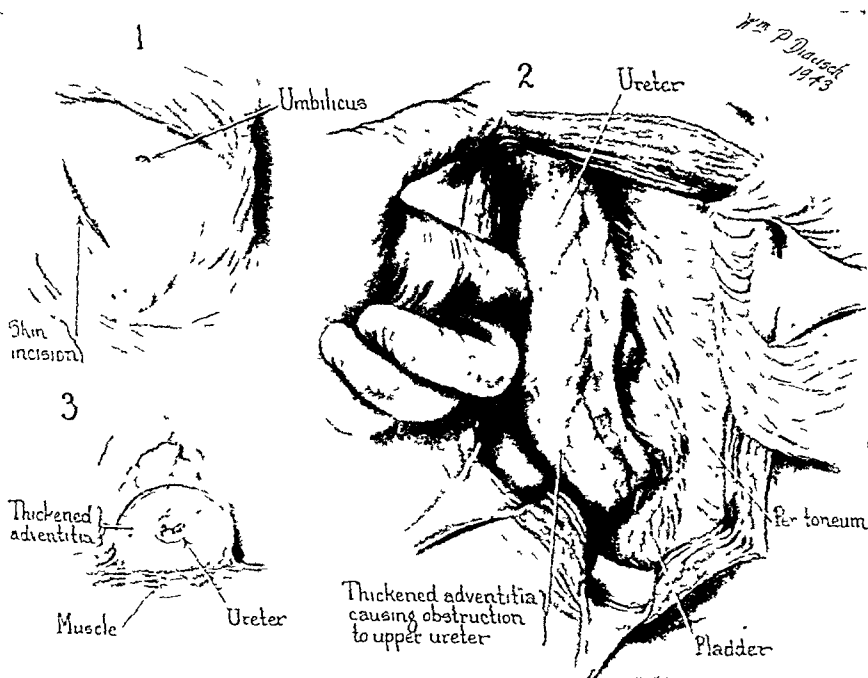


FIG 6 Case 3 Large mass with inlying, essentially normal ureter found at operation. pelvis and brought out through the incision for temporary diversion of the urine. This catheter was removed in a few days following which the ureterotomy healed promptly. Postoperatively the patient was followed for  $2\frac{1}{2}$  years during which time the hydronephrosis progressively receded and the kidney returned to normal (fig. 8). Pyelogram was reported by the roentgenologists as "within the limits of

normal." The patient's urine became free of leukocytes and cultures of the bladder urine on several occasions were sterile. There were no further symptoms suggestive of any urinary tract disorder.

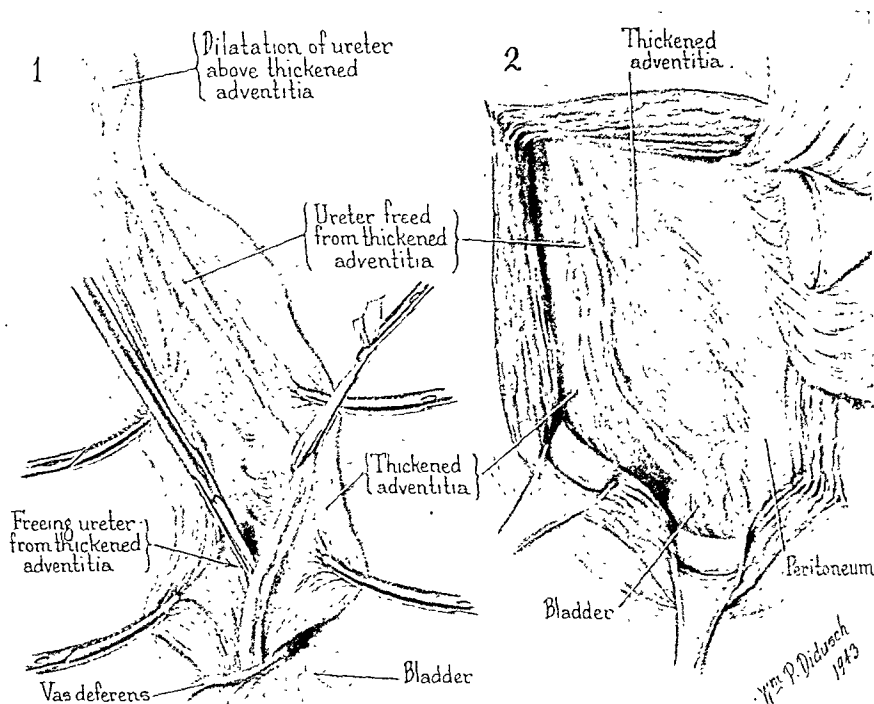


FIG 7. Case 3. Ureter being removed from compressing envelope from point just below kidney to just above bladder. Thick peri-ureteral covering was excised longitudinally to enable us to completely free ureter. Separation of ureter and hypertrophied adventitia was easy.



FIG. 8. Case 3. Retrograde pyelogram 6 months postoperatively showing that kidney had returned entirely to normal. Urine examination was negative and repeated cultures were sterile.

A fourth case of this unusual condition was encountered and again a successful result followed the separation of the ureter from the plastic envelope.

Case 4. R. G. P., Univ. of Va. Hosp. No. 226659, a man, aged 30, was admitted with a history of flank pain simulating right renal colic. The pain originated in

the right flank and radiated to the scrotum. He gave a past history of similar attacks over the course of a year in which he had been hospitalized on occasions at another institution for periods of several days during which time he received sedation. One episode of gross hematuria occurred and it was assumed that the patient had probably passed a calculus. X-rays taken elsewhere just before admission reported a possible calculus in the lower right ureter but a plain urogram at our hospital showed no shadows suggesting urinary calculus. The passage of ureteral catheters and various stone baskets to the renal pelvis after admission to our service failed to locate any evidence of calculus or obstruction. Excretory urograms indicated a normal left kidney giving an impression of hydronephrosis.

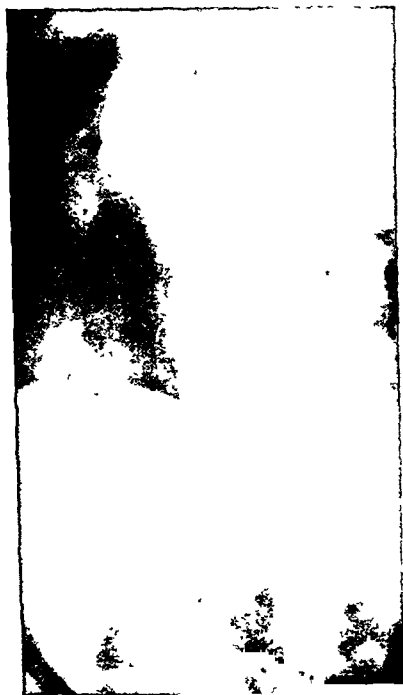


FIG. 9. Case 4. Retrograde pyelogram shows right hydronephrosis with non-filling of ureter beginning at point at about lower pole of kidney.

Retrograde pyelograms confirmed a definite obstruction in the right ureter beginning just below the ureteropelvic junction (fig. 9). The ureter failed to fill on retrograde injection from below. Ureteral catheters and Braasch bulbs were passed with ease to the right kidney on several occasions during the next 10 days but the flank pain continued to persist. The urine from the right kidney and bladder showed a few white blood cells. Cultures revealed *B. aerogenes* and *B. pyocyaneus*. The patient had not received chemotherapy prior to admission.

Because of the constant flank pain and some elevation of temperature, exploration of the right kidney and ureter was carried out. On exposure of the flank region, we again found the peculiar appearance of the ureter, as described in the

previous cases, to be present. The large ureteral mass resembled a garden hose and was easily lifted from its retroperitoneal location. It was found to be approximately 3 cm. in diameter. The ureteral mass, in this case, was not particularly adherent to the posterior peritoneum or lumbar muscles. On entering the mass through a longitudinal incision we found that the ureter was lying within a bed of plastic or hypertrophied tissue while the ureteral wall was only slightly larger than normal. An extension of the longitudinal incision into the peri-ureteral envelope enabled us to free the ureter down to the bladder and upward to the ureteropelvic junction (fig. 10). The ureter was separated or shelled out from the

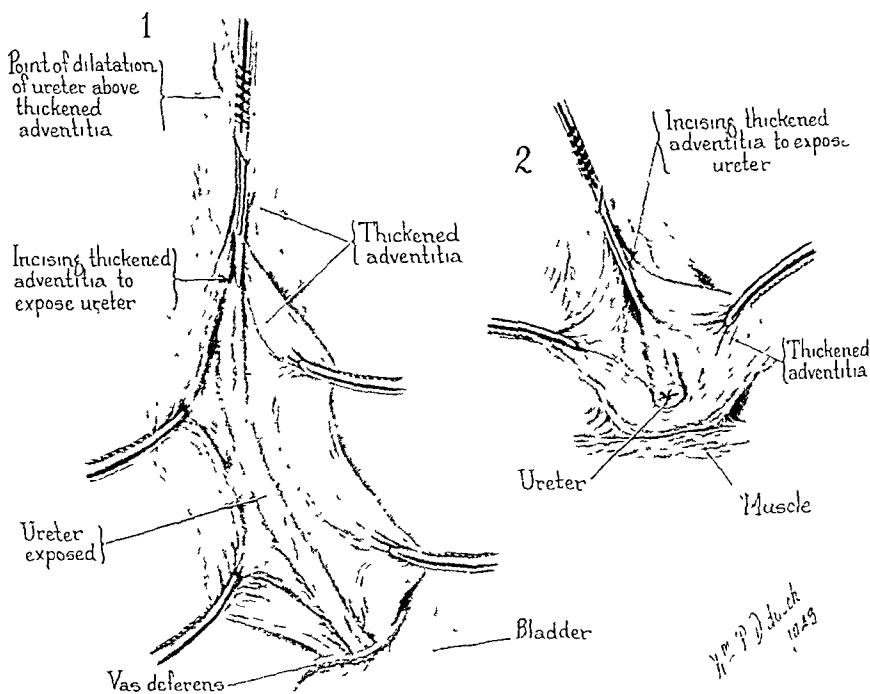


FIG. 10. Case 4. Longitudinal incision being made in greatly hypertrophied adventitia in order to free essentially normal underlying ureter and relieve compression.

envelope without difficulty. The lumen of the exposed ureter was then entered and a No. 12 Braasch bulb and No. 18 rubber catheter were passed to the bladder and the right kidney pelvis with ease without encountering any obstruction. After freeing the ureter completely from the thick peri-ureteral tissue, a No. 16 rubber catheter was inserted through the ureterotomy to the right renal pelvis. About two inches below this, we made another small ureterotomy and inserted a similar size catheter down to the bladder. The catheters were removed on the sixth postoperative day following which urine drained freely from the flank incision for only a few days. Healing was prompt and convalescence was uneventful. The patient has since had no further symptoms referable to the right kidney. Subsequent cystoscopies at the end of the second and third month postoperatively

revealed no right ureteral obstruction and a No. 12 Braasch bulb could be passed easily to the right renal pelvis. The hydronephrotic kidney returned to normal (fig. 11). Six months postoperative the patient reported that he was entirely well and would not consider any further cystoscopic examinations. He has remained asymptomatic to date.

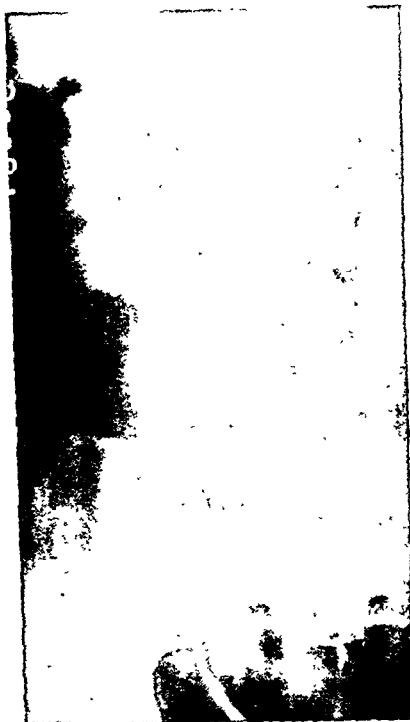


FIG. 11. Case 4. Retrograde pyelogram 3 months after ureterolysis shows essentially normal kidney and ureter except for slight dilatation of latter at point of ureterotomy. Patient was asymptomatic and urine almost free of leukocytes.

#### DISCUSSION

All of us have often encountered infected ureters in which the ureteral walls are thickened and inflamed with some degree of associated peri-ureteritis usually secondary to either primary renal or intraluminal inflammation. To encounter a remarkable degree of peri-ureteritis which by compression alone obstructs the ureter must be relatively rare even though we have experienced four cases.

From the information gained in the last 2 cases of this unusual peri-ureteral disease process, it is evident that had we carried out ureterolysis in case 1 and 2, we could have probably salvaged two kidneys which were unnecessarily sacrificed. It is in this respect that we hope that this report will be of benefit to others should they encounter similar cases of so-called "peri-ureteritis plastica."

It is indeed unfortunate in these two successfully treated cases that we failed to biopsy the peri-ureteral plastic tissue. It is, however, significant that in both of these cases the hydronephrotic kidneys returned to normal. In case 3, the

previous cases, to be present. The large ureteral mass resembled a garden hose and was easily lifted from its retroperitoneal location. It was found to be approximately 3 cm. in diameter. The ureteral mass, in this case, was not particularly adherent to the posterior peritoneum or lumbar muscles. On entering the mass through a longitudinal incision we found that the ureter was lying within a bed of plastic or hypertrophied tissue while the ureteral wall was only slightly larger than normal. An extension of the longitudinal incision into the peri-ureteral envelope enabled us to free the ureter down to the bladder and upward to the ureteropelvic junction (fig. 10). The ureter was separated or shelled out from the

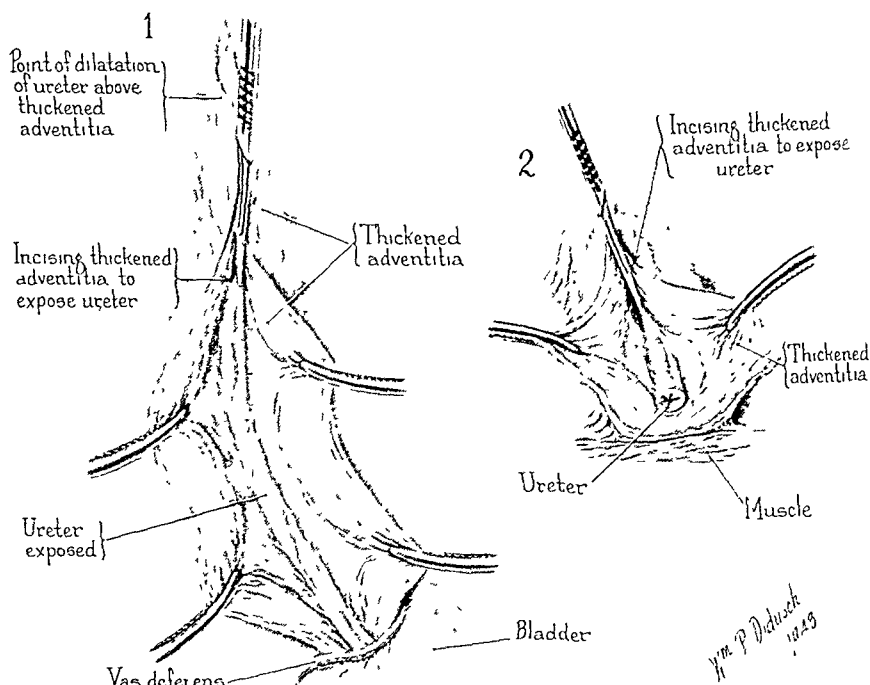


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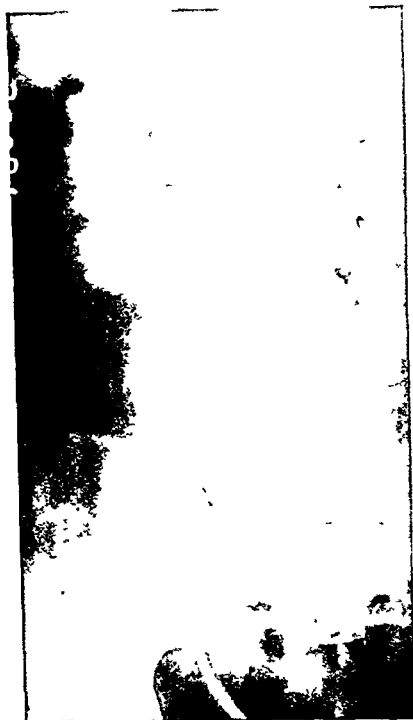


FIG. 11. Case 4. Retrograde pyelogram 3 months after ureterolysis shows essentially normal kidney and ureter except for slight dilatation of latter at point of ureterotomy. Patient was asymptomatic and urine almost free of leukocytes.

#### DISCUSSION

All of us have often encountered infected ureters in which the ureteral walls are thickened and inflamed with some degree of associated peri-ureteritis usually secondary to either primary renal or intraluminal inflammation. To encounter a remarkable degree of peri-ureteritis which by compression alone obstructs the ureter must be relatively rare even though we have experienced four cases.

From the information gained in the last 2 cases of this unusual peri-ureteral disease process, it is evident that had we carried out ureterolysis in case 1 and 2, we could have probably salvaged two kidneys which were unnecessarily sacrificed. It is in this respect that we hope that this report will be of benefit to others should they encounter similar cases of so-called "peri-ureteritis plastica."

It is indeed unfortunate in these two successfully treated cases that we failed to biopsy the peri-ureteral plastic tissue. It is, however, significant that in both of these cases the hydronephrotic kidneys returned to normal. In case 3, the



urine became entirely negative while in case 4, there was only an occasional leucocyte in the urine at the end of 6 months.

Speculation as to the pathogenesis of this disease process is of interest. From pathological examination, it is reasonable to assume that infection of some unknown type, probably occurring at some remote period, is the underlying etiological mechanism. In case 1, there was a past history of severe gonorrheal cystitis present for a number of years prior to the onset of the renal symptoms. There was also a history of two prostatic operations and the presence of gram positive cocci in the urine during a period when the patient had severe lower urinary complaints. Three years later, however, at the time the peri-ureteritis plastica condition was discovered, the urine was free of any cellular elements and infection, but bacterial stain of the removed peri-ureteral tissue revealed cocci to be present although they were absent in the urine or culture. In case 2 there was a sterile pyuria but no history of antecedent urinary tract infection. The onset was acute but according to the pathological condition present, the development of the peri-ureteritis was prior to the duration of the symptoms. One naturally thinks of the possibility of anerobic streptococci, pleuro-pneumonia, *B. influenzae*, *B. melitensis* or other unusual organisms which are not easily cultured. In case 3, a culture of non-hemolytic streptococci and *B. coli* were obtained during a period of previous lower urinary tract infection (cystitis). Unfortunately, the peri-ureteral tissue was not removed for biopsy and bacteriological stains. In case 4, cultures of *B. aerogenes* and *Pyocyanus* were reported. These may have overgrown any streptococci present. This case gave no history of previous lower tract disease.

In view of the foregoing findings, it is impossible to establish any single bacteriological common denominator, although from the above data one might consider an ascending streptococcal peri-ureteral infection from lower tract infection as the possible etiologic process. Streptococci are known to spread predominately through the lymphatics and the lesion present in these cases proved to be peri-ureteritis which we suspect resulted from a peri-ureteral lymphangitis that led to hypertrophic changes not unlike those seen in filarial lymphangitis.

The distribution of this inflammatory reaction in tissue surrounding the ureter would suggest a lymphatic origin. It was demonstrated years ago by Parker that the lymph channels pursue a longitudinal course in the adventitial coverings of the ureter. From their distribution in the loose adventitial tissues around the ureter they pass outward into the abdominal, common iliac, external iliac and hypogastric lymph nodes. Lymph channels coursing along the lower ureter in the adventitial coverings in some instances actually traverse the bladder wall before terminating laterally in the external iliac nodes.

There is also some experimental basis for the existence of anastomoses between the lymphatics of the bladder and lower genito-urinary tract with those in the adventitial coats of the ureter. Winsbury-White thoroughly demonstrated this by injections of dye particles into the base of the bladder and the cervical tissues of the female animal. Particles of dye and bacteria injected in this manner were traced in adventitial coverings of the ureter all the way to the kidney. Indeed, Kenneth Walker in the Hunterian Lecture of 1913 was able to trace the migration

of dye from the urethra to the upper ureter by way of the surrounding plexus of lymphatics. In his experiments, pigment injected into the base of the bladder could be seen 48 hours later in the loose tissue surrounding the muscular coat of the ureter. The peri-ureteral tissue was laden with inflammatory cells bearing particles of pigment with the main structures of the ureter consisting of muscular, submucous and mucous coats free of any invasion by the inflammatory cells or pigment. Pathways outside the ureter, therefore, exist for the ascent of infection which as in these cases may lead to a predominately peri-ureteral reaction.

It is of passing interest that in all 4 cases the right kidney was involved. Parker in her detailed study of the various sections of the ureter noted a difference between the distribution of the lymph collectors from the lower third of the human ureters on the right and left sides. Her work demonstrated, in general, that the lymphatics traversing the outside of the three sections of the ureters course upward and downward for a short distance and then enter the specific regional lymph nodes for each section. In her studies she noted that some of the channels from the lower third of the ureter on the right anastomose freely with lymph vessels from the middle third of the right ureter. Such a distribution or anastomosis does not occur on the left side and thus we can visualize infection originating primarily in the bladder or lower genito-urinary tract ascending in the peri-ureteral adventitial tissues more easily on the right because of this anastomosis. It is in the realm of possibility that this anatomic difference could account for the occurrence on the right side in all of the 4 cases reported.

One must consider in a process of this sort the possibility of the so-called "abortive infections" which have been well described following administration of various chemotherapeutic agents. We recently encountered 1 case of marked perirenal fibrosis in which an acute perirenal infection had evidently been aborted by treatment with a number of antibiotics. This mechanism, however, does not account for the type of tissue encountered in these cases because cases 2 and 3 did not receive any chemotherapy. The first and third patients in our series did receive sulfa drugs for a short period early in their medical treatment but not during any acute phase of urinary tract infection.

#### CONCLUSION

Four cases have been reported in which there was a peculiar, marked hyperplasia of the loose, areolar tissue surrounding the ureter.

This peri-ureteral tissue ranged from 1-2 cm. in thickness. It was so indurated and plastic in character so that we have termed the condition "peri-ureteritis plastica."

The peri-ureteritis gave the ureter the general appearance of a garden hose in the center of which the ureter was situated. The wall of the ureter was delineated or distinct from this hypertrophied adventitia.

The removed peri-ureteral tissue on microscopic study in two instances showed evidence of being chronic inflammation; cocci were seen in the stained peri-ureteral tissue in one of these cases.

Pathogenesis is speculative but the disease may begin as a peri-ureteral lym-

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This peri-ureteral plastic envelope compressed the ureter in all 4 cases producing hydronephrosis.

Two patients were treated by nephrectomy while in two others, the ureter was easily separated and freed from the peri-ureteral envelope. After freeing the ureter from this plastic peri-ureteral tissue, the compression was relieved and the obstructed kidneys returned to normal.

It is hoped that the successful therapeutic results following ureterolysis in the two last cases reported herein will encourage others to attempt renal salvage should they encounter similar instances of so-called "peri-ureteritis plastica."

*Charlottesville, Va. (S.A.V.)*

*Univ. of Alabama, Birmingham, Ala. (B.B.)*

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## URETERAL INJURIES IN GYNECOLOGIC SURGERY

EUGENE C. ST. MARTIN, BURDETTE E. TRICHEL, JAMES H. CAMPBELL AND  
C. M. LOCKE

The interest of the urologist in this subject arises from the desire to conserve renal function and to restore to the urinary tract continuity, adequate for the proper elimination of urine. The complications attending ureteral injuries constitute a real challenge to the surgeon performing gynecologic procedures, as well as to the urologist who is consulted to manage a plan of treatment.

### INCIDENCE OF URETERAL INJURIES

From November 1949, to June 1951, the Urology and Gynecology Departments of the Shreveport Charity Hospital collaborated in the study of the incidence of ureteral injuries in major gynecologic procedures. Preliminary excretory urograms were made on every patient undergoing major gynecologic surgery, exclusive of radical surgery for carcinoma of the cervix. Between the sixth and eighteenth postoperative day, all patients had cystoscopic examination to determine the patency of the ureters, stasis, and function. Retrograde and excretory urograms were performed on all questionable cases.

A total of 332 cases was thus studied with evidence of ureteral injury in eight cases, or 2.42 per cent. Five of the 8 cases were injuries considered due to minor trauma to the lower ureter, with resulting temporary hydronephrosis. In these cases, spontaneous regression occurred by the fifth week after surgery.

Three cases had complete unilateral ligation of the ureter. Of these, two were asymptomatic and were diagnosed by routine postoperative study.

It is of interest to note that in 36 patients, or 10.84 per cent of the 332 cases studied, definite hydronephrosis and hydro-ureter existed prior to surgery. In no case was the ureteral obstruction of such degree as to compromise renal function. Following gynecologic surgery, the urinary tract returned to a normal state in all except three. In these cases, urologic examination revealed complicating intrinsic ureteral disease of sufficient degree to account for the hydronephrosis and hydro-ureters.

From April 1950, to January 1952, a similar survey was made on patients undergoing radical surgery (the Wertheim-Taussig node dissection procedure) for carcinoma of the cervix. A significant increase in the incidence of ureteral injury was revealed (6 out of 20 cases, or 30 per cent). It is obvious, therefore, that this procedure constitutes a real hazard to the integrity of the urinary tract.

### MATERIAL FOR STUDY

During the past 3 years, we have had the opportunity to participate in the treatment of 26 cases of ureteral injury, secondary to gynecologic surgery. Five cases were from private practice. Twenty-one cases were treated in the Shreveport Charity Hospital. The latter group consisted of injuries from the surgery, gynecology, and tumor services of this hospital.

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 5, 1952.

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## TYPE OF GYNECOLOGIC PATHOLOGY

These injuries were associated with difficult gynecologic procedures for large fibroids, ovarian cysts and tumors, tubo-ovarian inflammatory masses, and carcinoma of the cervix.

## TYPE OF INJURY

The nature of these injuries varied from complete bilateral ligation to simple crushing. Unilateral obstruction, complete and incomplete, comprised 42.3 per cent of the injuries. Bilateral obstruction of varying degree was present in 6 cases.

## PRESENTING FINDINGS

The diagnosis was made at surgery in 7 cases. In 8 cases, the injury was *asymptomatic*. Postoperative anuria was present in 1 case and is pathognomonic of complete bilateral ureteral obstruction. The remainder of the cases were diagnosed from the investigation of unexplained fever, palpable mass, urinary fistula, and pyuria.

## MANAGEMENT; PRESENTATION OF CASES

Each injury was individualized and evaluated according to the time of recognition; type, extent, and location of injury; composition of suture; condition of the patient; and potential renal reserve. In each case, re-establishment of continuity of the urinary tract was attempted. Only in the hopeless case was the kidney sacrificed.

For ease of presentation, the injuries are grouped according to type of management with illustrative cases of particular interest:

- A. No treatment, observation, 6 cases.
- B. Postoperative ureteral dilatation, 2 cases.
- C. Indwelling catheter, 1 case.
- D. Uretero-ureteral anastomosis, 4 cases.
- E. Ureteral anastomosis to tube made from bladder flap, 1 case.
- F. Ureterovesical anastomosis, 5 cases.
- G. Deligation, 3 cases.
- H. Ureteral dissection, 1 case.
- I. Nephrostomy, ureter not repaired, 1 case.
- J. Nephrectomy, 2 cases.

*Case 1. Ureteral anastomosis to tube made from bladder flap.* G. A. 51-20295, aged 47, colored female. Shreveport Charity Hospital. On February 17, 1951, total hysterectomy and bilateral salpingo-oophorectomy were performed without difficulty. There was persistent, low grade fever postoperatively.

On the tenth day, the patient became slightly distended. At routine cystoscopy, a catheter could not be passed beyond 5 cm. on the right; a ureterogram revealed extravasation.

The eleventh day, a large mass was present, extending from the lower abdomen to the umbilicus. Excretory urograms (fig. 1, A) demonstrated this dramatically.

Through a Gibson's incision, 3600 cc of infected urine were removed from the extraperitoneal space. The proximal end of the ureter was easily located, but the distal end of the ureter could only be identified in a mass of scar tissue with the help of a large ureteral catheter inserted cystoscopically. As the dissection continued, a large retrovesical abscess was opened, precluding any desire to transplant the ureter into the bladder. An end to end ureteral anastomosis was thus done over a splint.

The procedure was not a success. A ureterocutaneous fistula persisted (fig. 2, B), and excretory urography revealed progressive loss of function. It was then decided to anastomose the lower ureter to a bladder flap tube by the method of Ockerblad. This was done on April 11, 1951. Urine drained from the wound for 18 days, when the fistula closed spontaneously.



FIG. 1. A, excretory urograms on tenth day after hysterectomy showing large extra-peritoneal mass. B, cutaneous fistula after uretero-ureterostomy. C, excretory urograms, 1 year, after anastomosis of ureter to tube from bladder flap.

The mild right hydronephrosis gradually subsided, and 6 months later the excretory urograms were normal (fig. 1, C).

*Case 2. Ureterovesical anastomosis.* A. L. O., aged 49, a Negress, underwent radical hysterectomy with node dissection at Shreveport Charity Hospital, April 22, 1950 for carcinoma of the cervix. One month later, cystoscopy revealed a vesicovaginal fistula. This incorporated the intramural portion of the right ureter in its wall. There was progressive hydronephrosis. Seven weeks from the original surgery, the right ureter was re-implanted transperitoneally into the bladder and a successful combined transvesical and transvaginal closure of the fistula was obtained. One year later, June 21, 1951, the pyelograms were normal, the urine negative.

*Case 3. Deligation.* E. M., 541849, aged 49, a Negress, entered Shreveport Charity Hospital. On February 25, 1950 total hysterectomy and bilateral salpingo-oophorectomy were performed. Preoperative excretory urograms were normal. Difficult bleeding was encountered in the right broad ligament during

removal of a large right interligamentary tumor. At routine cystoscopy on the seventeenth postoperative day, neither ureteral catheter nor injected dye would traverse beyond 4.5 cm. on the right. Excretory urograms revealed an enlarged, functionless right kidney and a normal left (fig. 2, A). The patient was asymptomatic and afebrile.

On the nineteenth day, a nephrostomy was done in an attempt to salvage the kidney. There was prompt return of function.

On the forty-fourth day, after repeated attempts to catheterize the ureter cystoscopically were unsuccessful, a transperitoneal exploration of the lower right ureter was performed. The intact ureter was tediously dissected from a dense bed of scar tissue. Then a No. 8 ureteral catheter was passed cystoscopically and left indwelling for 10 days.

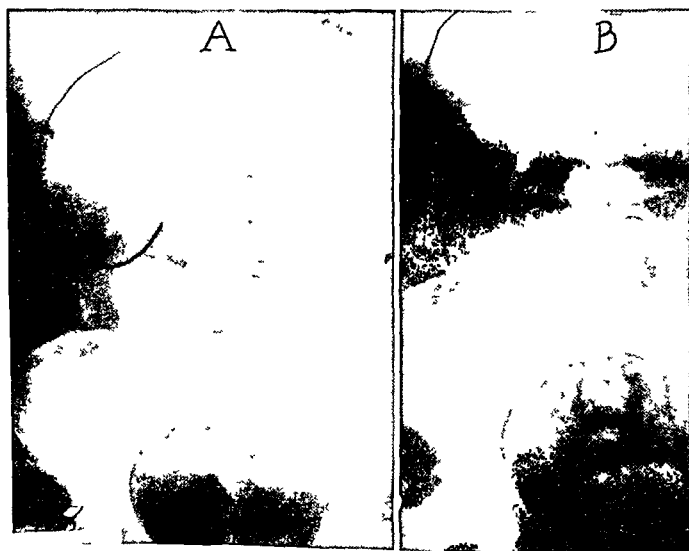


FIG. 2 A, enlarged, nonfunctioning right kidney 18 days after operation. B, excretory urograms, 1 year post deligation. Renal function good; mild hydronephrosis

The nephrostomy tube was removed shortly thereafter. Ureteral dilatations were later done in the out-patient clinic. One and two year excretory urograms revealed a mild residual hydronephrosis with good function (fig. 2, B). The upper ureter has remained slightly dilated and tortuous. The urine is negative.

*Case 4. Ureteral dissection.* L. S., aged 40, a white female, entered Shreveport Charity Hospital. The diagnosis was carcinoma-in-situ of the cervix. A total hysterectomy was performed on January 6, 1949. In the early postoperative period, a lower nephron syndrome developed from two severe transfusion reactions. Recovery was slow, the nonprotein nitrogen and creatinine having reached 191.8 and 15.5 mg. per cent respectively.

Urological investigation for a urinary fistula was done April 4, 1949. Left nephrocalcinosis had developed with no function demonstrable by excretory urograms (fig. 3, A). There was a right hydro-ureter and hydronephrosis. A

catheter could not be passed up the left ureter. It was apparent that the patient had sustained serious ureteral injury during the hysterectomy, as well as the transfusion reactions. Although the nonprotein nitrogen was now 47.4 mg. per cent, surgical intervention was not advised.

The patient was re-admitted to the hospital on January 30, 1950, for repair of a large ventral hernia. There was re-evaluation of the status of the urinary tract. Slight but unexpected function was detected in the left kidney. There was constant seepage of urine. Neither a ureterovaginal nor vesicovaginal fistula could be demonstrated. Because of this urinary seepage and because of the persistent hydro-ureters, both lower ureters were dissected transperitoneally during repair of the hernia. There was marked peri-ureteral fibrosis. A fistula was not detected, yet no urinary seepage occurred after the operation. Catheters could be inserted easily, now, up the left ureter (fig. 3, B).



FIG. 3. A, excretory urograms. No function of left kidney, 9 months. B, left pyelo-ureterogram, 1 year. C, excretory urograms, 2 years, improving function, left kidney.

There has been progressive increase in function of the left kidney as determined by excretory urography (fig. 3, C), and dye tests, despite the nephrocalcinosis. She is asymptomatic, has a normal blood pressure and urinalysis. The nonprotein nitrogen is 41 mg. per cent, the blood urea nitrogen 20.2 mg. per cent.

#### DISCUSSION

In 26 cases of ureteral injuries seen in the past 3 years, no deaths have occurred. The end results have been good in 20 patients, fair in 1, and failures in 4 patients (table 1). Two patients have been lost to follow-up, in one of whom an impassable ureteral stricture developed and that case must be considered a failure.

It is believed that in at least 8 cases, sacrifices of the kidney might have been justified except from the conservative urologic approach. In each of these cases, the kidney has been restored to valuable use, not a liability, but an asset. Such results justify faith in the ability of the kidney to recover from injury.

There have been two nephrectomies, both as the procedure of choice and not secondary to a failure at repair of the injury.

The interval between injury and final operation has varied from the recognition at the time of initial surgery to 13.5 months. Good results have been attained in injuries repaired 42, 53, and 414 days from the date of injury. Temporary urinary diversion with definitive ureteral management, 42, and 44 days postoperatively, has produced good results.

An interesting case, No. 1, has been presented with success in the use of the bladder tube flap after initial failure of an uretero-ureteral anastomosis. In another case, No. 3, the kidney has made an excellent recovery after apparently complete ligation for 19 days. Nephrocalcinosis developed in case 4 for which an adequate explanation is lacking. This kidney also showed marked return of function after dissection of the lower ureter from a dense bed of scar tissue.

TABLE 1

| TREATMENT                             | RESULTS |      |         |              |
|---------------------------------------|---------|------|---------|--------------|
|                                       | Good    | Fair | Failure | No follow up |
| 1. No treatment                       | 5       |      |         | 1            |
| 2. Ureteral dilatation, postoperative | 1       |      | 1       |              |
| 3. Inlying catheter, crush            | 1       |      |         |              |
| 4. Uretero-ureteral anastomosis       | 3       |      | 1       |              |
| 5. Bladder tube flap                  | 1       |      |         |              |
| 6. Ureterovesical anastomosis         | 4       | 1    |         |              |
| 7. Deligation                         | 2       |      |         |              |
| 8. Ureteral dissection                | 1       |      |         |              |
| 9. Nephrostomy, ureter not repaired   |         |      | 1       |              |
| 10. Nephrectomy                       | 2       |      |         |              |
| 11. Ligation, election to leave       |         |      | 1       |              |
| Total                                 | 20      | 1    | 4       | 1            |

The failure in 1 case, in which a uretero-ureteral anastomosis was performed, might be explained on inadequate splinting and failure of the patient to return for necessary ureteral dilatations. In 2 cases neglect in making proper disposition of an extensive ureteral stricture, secondary to the Wertheim procedure, resulted in autonephrectomy. Failure to deligate the second of a bilateral ureteral ligation resulted in the spontaneous development of a urinary fistula.

The occasion for the opportune use of ureterosigmoidostomy or of cross uretero-ureterostomy has not been encountered in this series.

#### CONCLUSIONS

After an adequate evaluation of this series of ureteral injuries, the following conclusions have been reached: 1) The use of prophylactic ureteral catheterization in difficult gynecological procedures, avoidance of stripping of the ureter's blood supply, and careful reperitonealization will prevent many injuries. 2) Palpation of the renal areas for tenderness should be as routine in the postoperative

patient as palpation for calf tenderness. 3) Asymptomatic injuries can be diagnosed by more frequent use of urography. These injuries constituted 30.7 per cent of this series. 4) Early diagnosis, adherence to the basic urological principles of adequate splinting and drainage, control of infection, and close follow up are important factors in the success of any plan of management. 5) The extensive fibrosis secondary to ureteral ischemia from the Wertheim-Taussig operation must be observed closely. Definitive early treatment of the lower ureter is imperative when cystoscopic ureteral dilatation cannot be accomplished, as autonephrectomy is a common sequela. 6) Uretero-ureteral anastomosis should not be attempted when the distal stump is damaged; splinting for a minimum of 3 weeks is advisable when this procedure is used in the severed ureter. Periodic cystoscopic dilatation to avoid stricture is mandatory. 7) Re-implantation into the bladder gives consistently good results and is the procedure of choice when the terminal ureter is injured, and where the bladder can be reached without tension. 8) Deligation has been used both in the immediate and late postoperative periods; it is technically much easier after preliminary diversion of the urinary stream. The latter combination is the procedure of choice in the acutely ill patient with unilateral or bilateral, complete ureteral ligation. 9) Cystoscopy is a helpful adjunct to surgical management. 10) Intentional ureteral ligation is a hazardous procedure. Palpation of the opposite kidney is inadequate to evaluate unknown renal reserve. Excretory urography on the operating table is recommended when available, for maximum information. 11) Surgical injury of the ureter is no longer a catastrophe. Whereas, the immediate results of conservative surgical repair may be disheartening, the late results are good in most instances and justify the attempts to conserve renal function and structures, and to re-establish continuity of the urinary tract.

#### SUMMARY

The incidence of ureteral injury in 332 patients undergoing major gynecologic surgery, exclusive of radical surgery for carcinoma of the cervix, was 2.42 per cent. In 20 patients on whom the Wertheim-Taussig node dissection was performed for carcinoma of the cervix, the incidence of injury was 30 per cent.

A series of 26 cases of ureteral injuries have been presented. The results were good in 20, fair in 1 and failures in 4. One patient was lost to adequate follow up. There were no deaths.

*101 Medical Arts Bldg., Shreveport, La. (E. C. St. M., J. H. C.)*

*1030 Highland Ave., Shreveport, La. (B. E. T.)*

*Shreveport Charity Hospital, Shreveport, La. (C. M. L.)*

## PHYSIOLOGY OF THE URETERO-INTESTINAL ANASTOMOSIS: II. INHIBITORY EFFECT OF CORTISONE ON STRICTURE FORMATION

ROGER BAKER, DUNCAN GOVAN, JOHN HUFFER AND JAMES CASON

*From the Department of Surgery (Division of Urology), the University of Chicago  
Chicago, Ill.*

Despite the expenditure of enormous sums of money and millions of man-hours for cancer research, surgery remains as the only method known to cure bladder cancer. It has been proven that radical surgery will produce the greatest rate of cure for early cancer. This principle has been applied successfully to early carcinoma of the colon, breast and lung. Total cystectomy, rather than local tumor excision by transurethral or suprapubic resection, should yield the greatest rate of cure for early bladder cancer. A unique exception to this principle is observed occasionally in a small percentage of patients with bladder cancer who may be treated for a prolonged period of time by local excision of the tumor. Unfortunately, not only is it impossible to determine prior to treatment those patients comprising this group, but also the majority of these patients die from recurrence of the malignancy.

Cystectomy is not a difficult operation. Most practicing urologists, however, do not perform cystectomy for early bladder cancer. The majority of those urologists who formerly did perform cystectomy have discontinued use of the operation or only perform cystectomy with reluctance. As a consequence the cure rate of cancer of the bladder is considerably lower than it should be. Dissatisfaction with the procedure is due to the high incidence of serious renal disease subsequent to diversion of the urinary stream to skin or bowel.

Many urologists are reluctant to publish or discuss their unsatisfactory results following cystectomy. This attitude is apparently predicated on the assumption that the unsatisfactory results obtained in their hands with this procedure are based entirely on poor surgical technique. This impression is re-inforced further by the publications of a few urologists reporting only excellent results following ureterocutaneous or uretero-intestinal anastomosis. This is an unrealistic viewpoint. There are too many highly capable urological surgeons describing dissatisfaction with the operation and its renal sequelae for this problem to be solely the product of poor surgical technique. It may be conservatively phrased that no one operator or institution has solved or prevented the renal disease that frequently follows uretero-intestinal anastomosis.

The relative and absolute incidence of cancer of the bladder is increasing. Cystectomy should be performed for early bladder cancer. Other types of pelvic cancer also dictate excision of all pelvic organs including the bladder. In order to obtain the maximum yield of cure of early bladder cancer, and until a medical

This investigation was aided in part by an American Cancer Society Institutional Grant. Read at annual meeting, American Urological Association, Atlantic City, N. J. June 25, 1952.

cure of cancer be developed, it is important that surgeons be able to perform cystectomy without fear of serious or fatal renal complications. A successful uretero-intestinal anastomosis would eliminate or reduce to a minimum the incidence of secondary renal disease so that this end may be realized.

Probably the most important contribution toward solution of this problem was the investigation of Hinman and Weyrauch in 1942.<sup>1</sup> Their study consisted of uretero-intestinal and ureterovesical implantation in dogs. It was observed that healing at the stomal site occurred either by primary union and early epithelialization (re-anastomosis of ureter to bladder), or by granulation and cicatrization and late epithelialization (uretero-intestinal implantation). The latter condition obtained in the presence of infection and the dogs developed stricture, hydronephrosis, hydronephrosis and pyelonephritis.

This experimental demonstration of peri-ureteral concentric fibrosis and stricture at the area where ureter traverses bowel wall has great clinical significance. Thomas<sup>2</sup> reports that of 36 patients having uretero-intestinal implantation, six had bilateral and five had unilateral uretero-intestinal stricture. Forty-four per cent of patients in this group had pyelonephritis and two became uremic. Harvard and Thompson<sup>3</sup> report that 88 per cent of 144 patients subject to uretero-intestinal implantation had obstructive phenomena as determined by excretory urograms. Sixty-five per cent of deaths were due to renal disease. Dean<sup>4</sup> observed that over 58 per cent of patients in his series of 89 uretero-intestinal anastomoses had obstruction of the upper urinary tract shown by excretory urograms. Twenty per cent of the 98 patients required secondary operation for faulty anastomosis.

Reference to the experimental study of Hinman and Weyrauch<sup>1</sup> suggests that if postoperative connective tissue hyperplasia could be inhibited, these structures so frequently observed at the uretero-intestinal anastomosis might be prevented or reduced.

Ragan and his associates,<sup>5</sup> and also Spain and Molomut<sup>6</sup> have demonstrated that by systemic use of cortisone, connective tissue formation could be inhibited in experimentally produced wounds. Baker and Whitaker<sup>7</sup> performed similar experiments and illustrated that the retardation of connective tissue growth could be elicited by direct topical application of adrenal cortical extract, indicat-

<sup>1</sup> Hinman, Frank and Weyrauch, H. M.: An experimental study of uretero-intestinal implantation. *Surg., Gynec. & Obst.*, 74: 129, 1942.

<sup>2</sup> Thomas, G. J., Malcolm, D. C. and Bischoff, A. J.: Cystectomy and urinary diversion in carcinoma of bladder. *J. Urol.*, 65: 553, 1951.

<sup>3</sup> Harvard, B. M. and Thompson, G. J.: Congenital exstrophy of the urinary bladder. *J. Urol.*, 65: 223, 1951.

<sup>4</sup> Dean, A. L.: The upper urinary tract following ureterointestinal anastomosis for bladder tumors. *J. Urol.*, 63: 858, 1950.

<sup>5</sup> Ragans, C., Harvey, E. L., Platz, C. M., Meyer, K. and Blunt, J. W.: Effect of cortisone on production of granulation tissue in a rabbit. *Proc. Soc. Exper. Biol. & Med.*, 72: 718, 1949.

<sup>6</sup> Spain, D. M. and Molomut, N.: Effect of cortisone on formation of granulation tissue in mice. *Am. J. Path.*, 26: 710, 1950.

<sup>7</sup> Baker, B. L. and Whitaker, W. L.: Interference with wound healing by the local action of adrenocortical steroids. *Endocrinology*, 46: 544, 1950.



ing that the response was a specific one, and not due to a generalized tissue reaction. Stinchfield,<sup>8</sup> in an experimental study of dog arthroplasties, administered cortisone locally and systemically and demonstrated a marked reduction in fibrous tissue formation postoperatively in the operative site. Rosenberg<sup>9</sup> administered cortisone to a series of rabbits and observed a diminution in scar tissue and contracture in the esophagus after the production of localized sodium hydroxide burns. These results suggest that cortisone administration might have an inhibitory effect on the connective tissue hyperplasia that occurs at the stomal site of uretero-intestinal implantation. Consequently, an experimental study is presented on the inhibitory effect of cortisone on stricture formation following ureterosigmoid and ureterovesical anastomosis.

#### EXPERIMENTAL

*Procedure.* The experimental animals were divided into two main groups, 6 dogs being used for each group. All surgical procedures were performed on healthy male or female mongrel dogs using intravenous seconal anesthesia while observing usual aseptic precautions. No attempt was made preoperatively to clean or sterilize the bowel by the use of cathartics, enemas or intestinal antibiotic drugs. Cortisone\* (Cortone) was administered intramuscularly, 50 mg. daily, to three dogs in each group, for 21 days postoperatively. Three dogs in each group served as controls.

Group I (ureterosigmoidostomy): Six dogs were prepared as follows: Through a right paramedian incision, the bladder, ureters and sigmoid colon were visualized. The ureters were divided 1 cm. from the ureterovesical junction and the distal stumps ligated. A 1.5 cm. longitudinal incision was made in the end of the proximal segment of the ureter on the dorsal aspect, and a 00 silk ligature inserted. A 1 cm. incision was then made in a segment of the sigmoid colon that rested in line with the direction of the ureter. The incision was carried through the serosa and muscularis to expose the mucosa. Through a small opening in the mucosa at the distal end of the incision, the free ends of the ureteral ligatures which were threaded on large curved needles, were introduced into the lumen of the bowel and brought out through the bowel wall 1.5 cm. distal to their point of entry. Tension on the ligatures caused the ureter to enter the lumen of the bowel and the sutures were tied. Serosa and muscularis were approximated over the ureter with three interrupted 00 silk sutures, constructing a generous ureteral trough.

Postoperatively three of these dogs received cortisone. Three dogs serving as controls received no cortisone. None of the dogs were given antibiotic drugs during preoperative or postoperative periods.

Group II (re-anastomosis of ureter to bladder): Six dogs were prepared as follows: The bladder and ureters were exposed through a right paramedian

<sup>8</sup> Stinchfield, F. E.: Experimental and clinical use of oxidized cellulose and cortisone in the prevention of excess bone and fibrous tissue formation. *J. Bone & Joint Surg.*, **32**: 739, 1950.

<sup>9</sup> Rosenberg, N., Kunderman, P. J., Vroman, L. and Mooltan, S. E.: Prevention of experimental lye strictures of the esophagus by cortisone. *Arch. Surg.*, **63**: 147, 1951.

\* Cortone kindly supplied by Dr. Augustus Gibson, Merck and Company.

incision. The ureters were divided and the distal ends ligated. The ureters were introduced individually into the bladder through separate stab wounds and held in place by means of a single silk suture. Postoperatively three of these dogs received cortisone. Three dogs serving as controls received no cortisone. No antibiotic drugs were given postoperatively.

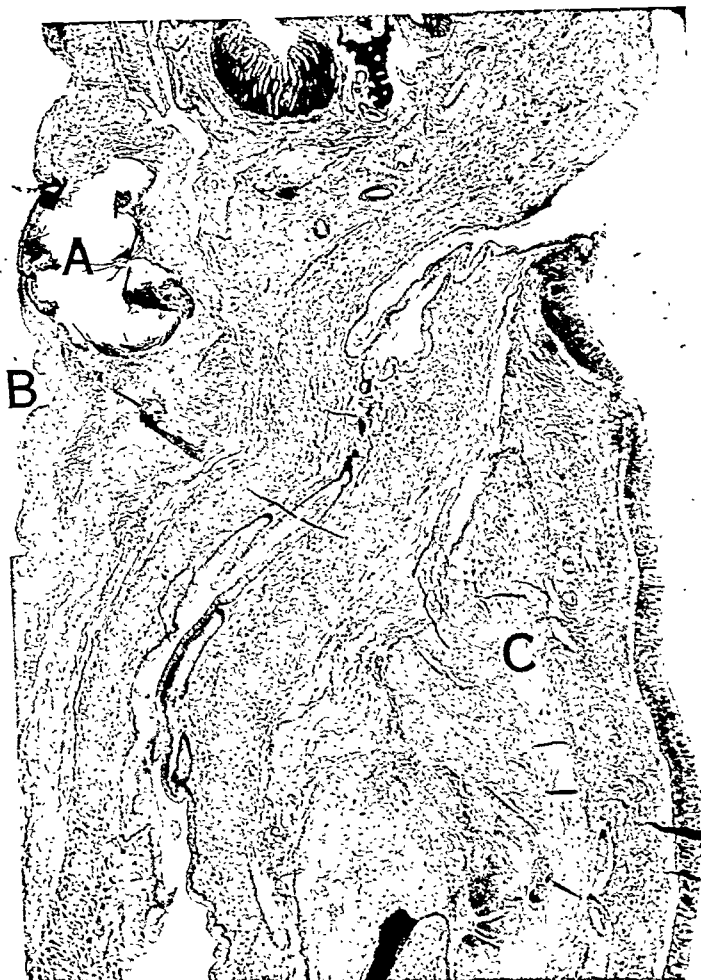


FIG. 1. Uretero-intestinal anastomosis of a cortisone-treated dog 115 days subsequent to operation. Observe: Minimal fibrous tissue reaction at site of anastomosis; minimal amount of scar tissue about suture (A); serosa (B) and muscularis (C) of colon. X11.

*Results.* Group I (ureterosigmoidostomy): The three cortisone treated dogs were sacrificed 45 to 115 days postoperatively. All uretero-intestinal stomas were patent and the kidneys were grossly normal. Microscopic examination revealed no evidence of excessive connective tissue proliferation or stricture at the uretero-intestinal anastomosis (fig. 1). Glandular metaplasia of the transitional epithelium in the terminal ureter was observed in one dog.

Two of the control dogs were sacrificed 45 to 115 days postoperatively.

Obstruction at the uretero-intestinal stomas, hydroureter, hydro-nephrosis, pyonephrosis and/or pyelonephritis were observed. Microscopic examination demonstrated the marked fibrous tissue hyperplasia at the uretero-intestinal anastomosis (figs. 2,4). Comparison photomicrographs of the anastomotic site strikingly demonstrate the marked increase of scar tissue of the control dogs versus the experimental groups (fig. 3).

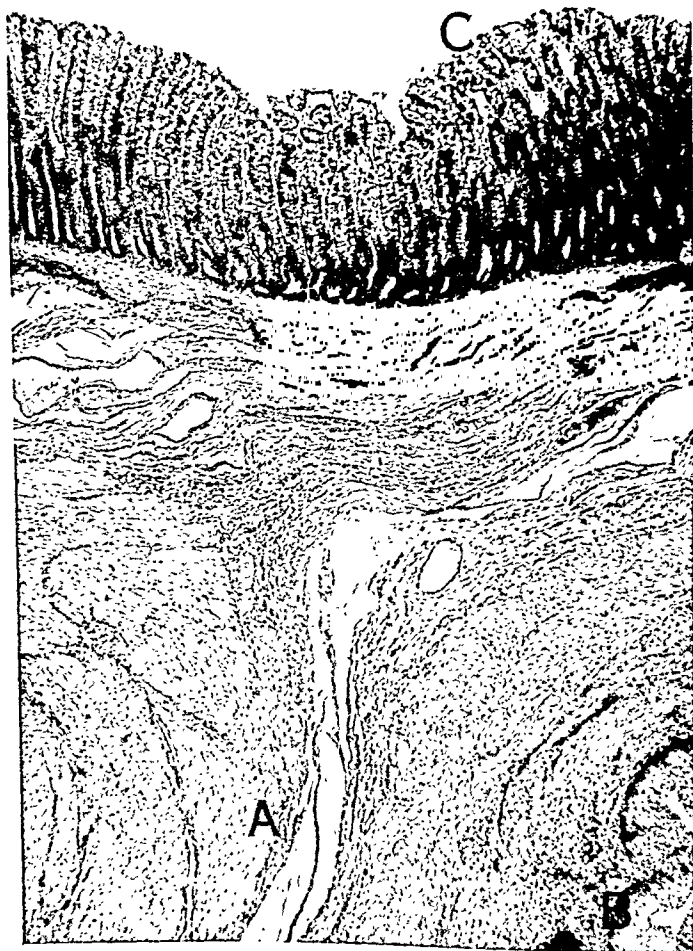


FIG. 2. Uretero-intestinal anastomosis of a control dog 115 days subsequent to operation. Observed marked deposition of fibrous tissue (A) about ureter (B) as it traverses wall of colon approaching mucosa (C). X55

The third control dog died 4 days after operation of septicemia from a wound abscess.

Group II (re-anastomosis of ureter to bladder): These dogs were sacrificed 45 to 115 days postoperatively. No significant changes, gross or microscopic, were noted in the ureterovesical anastomoses, ureters and kidneys of either the cortisone-treated or control dogs (fig. 5).

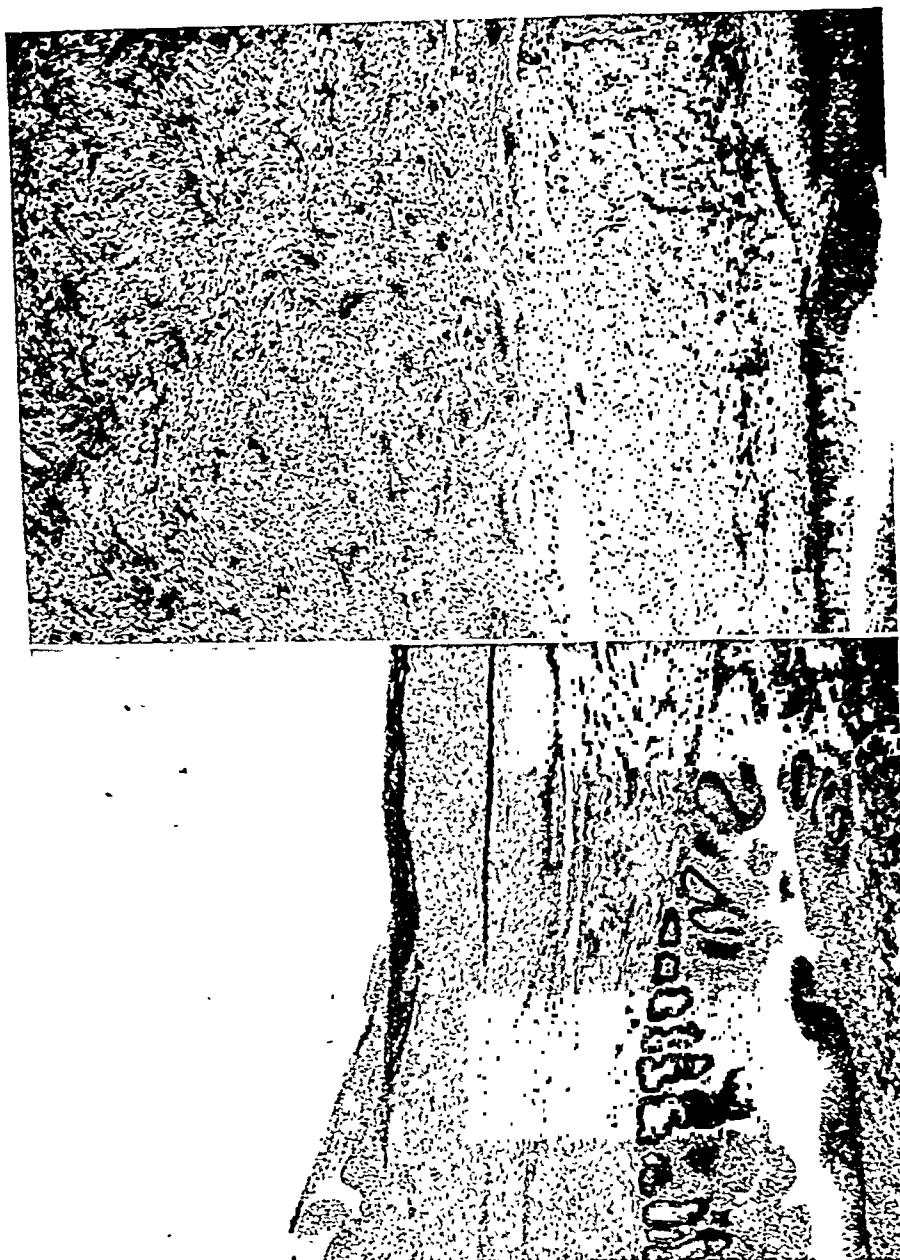


FIG. 3. (Upper) comparison photomicrographs demonstrating difference in quantity of scar tissue deposited at uretero-intestinal anastomosis in cortisone treated (upper) and control dog (lower).  $\times 65$ .

#### CLINICAL APPLICATION

The experimental results observed prompted a clinical investigation. The effect of the systemic administration of cortisone on postoperative connective tissue hyperplasia at the uretero-intestinal anastomosis has been studied thus far on

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#### CLINICAL APPLICATION

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12 humans. Prior to operation, each patient received routine bowel preparation for intestinal surgery, i.e., laxatives, enemas, and intestinal antibiotic drugs. These antibiotic drugs were continued for 3 weeks following surgery. All patients had a modified Coffey I uretero-intestinal anastomosis with construction of a short submucous tunnel.

Two patients received intramuscular injections of cortisone, 50 mg. twice daily, for 21 days postoperatively. Ten other patients received cortisone, 100 mg. intramuscularly twice daily, for 2 days prior to surgery and then 75 mg, twice daily, for 21 days. In view of recent observations on cortisone therapy it



FIG. 4. Uretero intestinal stoma of control dog 115 days subsequent to bilateral uretero intestinal anastomosis. Note ureter traversing bowel wall (A), marked fibrous tissue growth in peri ureteral area (B), reaction about suture (C) and normal intestinal mucosa (D)  $\times 26$ .

would appear advisable to gradually reduce the dose of cortisone at the end of 3 weeks instead of abruptly discontinuing the drug.

During the postoperative period one patient developed some separation of the abdominal wound that did not require surgical attention. Chromic catgut had been used in this patient to approximate rectus fascia. All subsequent patients receiving cortisone postoperatively have had steel wire closure of the entire abdominal wall.

The 12 patients operated upon have been studied for 4 to 14 months postoperatively. Serum electrolytes and carbon dioxide combining-power are normal. Although each patient did not receive any antibiotic drugs after discharge from the hospital, none developed clinical signs or symptoms of pyelonephritis. None have died from renal disease.

Excretory urograms illustrate normal upper urinary tract patterns indicative of the absence of ureteral stricture (fig. 6). It would appear that connective tissue hyperplasia with secondary stricture formation at the uretero-intestinal anastomosis has been inhibited as a result of the postoperative administration of cortisone.



FIG. 5. Stoma of ureterocystoneostomy from cortisone-treated dog, 115 days subsequent to operation. Observe patency of stoma, absence of abnormal quantity of fibrous tissue, and normal pattern of ureter and bladder.  $\times 29$ .

Two patients have died, one from extension of the neoplasm and the other from tumor recurrence. At the time of operation one of these patients had moderate hydro-ureter and hydronephrosis as a result of partial occlusion of the ureterovesical orifice by tumor tissue. Autopsy specimens demonstrated patent anastomoses of ureter to bowel, normal caliber ureters, normal renal pelvises and calyces and absence of pyelonephritis. In the two patients completely studied, a



uretero-intestinal valve has been created by the use of cortisone that was apparently giving full protection to the upper urinary tract.

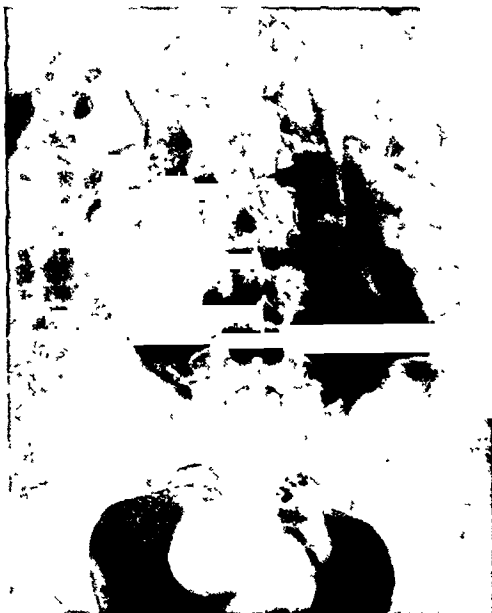


FIG. 6. J. C. Excretory urogram taken 8 months subsequent to bilateral ureterosigmoidostomy for carcinoma of bladder. Apparently no stricture formation at uretero-intestinal stomas as evidenced by normal upper urinary tracts. Cortisone administered postoperatively.

#### DISCUSSION

Reference to the results observed in this investigation reveal that the most significant feature is the absence of excessive connective tissue formation with secondary strictures at the uretero-intestinal anastomosis in the dogs that received systemic cortisone postoperatively. In sharp contrast to this, marked fibrous tissue hyperplasia with scarring occurred at the uretero-intestinal anastomosis in all dogs not receiving cortisone. The hydronephrosis that results from an anastomotic stricture in the control dog has been compared with the normal kidney in the cortisone treated dog without anastomotic stricture.

It is believed that this beneficial effect of scar tissue inhibition in the healing wound by use of cortisone is observed only in the presence of infection. Confirmation of this impression may be obtained by examination of the results following re-anastomosis of ureter to the uninfected bladder. Few contrasting gross or microscopic changes occurred in the quantity of scar tissue deposited in the healing wounds of these dogs. There was no significant variation in the postoperative growth of connective tissue at the ureterovesical anastomosis between the cortisone-treated and control dogs. Healing occurred by primary union and early epithelialization instead of by scarring and late epithelialization as observed in the anastomosis of ureter to fecally-infected colon. The only variable factor was infection.

As a result of these experiments it may be concluded that cortisone does not reduce the normal amount of fibrous tissue in a normally healing wound. Infection in a healing wound, however, acts as a stimulus for increased local deposition of fibrous tissue. Apparently cortisone modifies or reduces this fibroplasia or stimulus-producing fibroplasia in the infected healing wound. This observation has been confirmed further by additional data on the prevention and treatment of other strictures of the urological tract to be published elsewhere.<sup>10</sup>

It would appear to be of importance therefore to reduce to a minimum bowel infection during the reparative stage by administering intestinal antibiotic drugs until complete healing of ureter to bowel has been effected. It has been determined previously that although cortisone retards fibroplasia in wounds, a firm union is effected by a maximum of three weeks. Cortisone and intestinal antibiotics may probably be safely discontinued at that time without subsequently developing a uretero-intestinal stricture. The precise dosage of cortisone necessary to effect maximum reduction in scar tissue is unknown and must be deferred pending further clinical investigation of additional patients and long-term evaluation of those patients already treated.

In view of the finding that stricture formation has been prevented at the uretero-intestinal anastomosis in the experimental animal by use of cortisone, additional investigations are underway exploring the possibility of constructing a competent uretero-intestinal valve.

#### SUMMARY

Connective tissue hyperplasia with secondary stricture formation, which frequently occurs at the site of the anastomosis following uretero-intestinal implantation in the presence of infection, has been significantly reduced in the dog by the systemic use of cortisone postoperatively.

Cortisone administration to dogs following re-anastomosis of ureter to bladder caused no appreciable gross or microscopic quantitative changes in fibrous tissue deposition at the ureterovesical anastomosis. This effect is probably due to the absence of infection in these dogs.

Results in the clinical cases are not conclusive due to the limited number of patients studied thus far. The results do indicate that there has been minimal postoperative connective tissue hyperplasia at the uretero-intestinal anastomosis in the 12 patients treated as determined by absence of hydro-ureter and hydro-nephrosis on intravenous pyelograms. In two of these patients this observation has been confirmed by microscopic examination.

As a result of this investigation it would appear that cortisone exerts no effect on fibroplasia in the uninfected healing wound. Cortisone apparently reduces the increased fibroplasia and scar usually observed in the presence of infection, thereby permitting only normal fibrous tissue deposition at the uretero-intestinal anastomosis.

<sup>10</sup> Baker, R., J. Huffer and D. Govan: The effect of cortisone on strictures of the urological tract. Surg., Gynec. and Obst., In press.

## INDICATIONS FOR URETERO-INTESTINAL ANASTOMOSIS

CHESTER A. FORT

*From the Department of Urology, Emory University School of Medicine, Atlanta, Ga.*

With the recent wave of enthusiasm shown over uretero-intestinal anastomosis, I thought it might be well to review the indications for this procedure.

We are familiar with the occasional emergency which arises, usually during some type of pelvic surgery or injury, in which the ureter is divided. There are also occasions in which the diversion of the urinary stream is necessary in cases of carcinoma of the cervix, with metastasis, or malignancies arising in the pelvis in which the lumens of the ureters are obstructed. It is not my intention to deal with these occasional cases, but rather to deal with those which are more elective, and the ones which the urologist more often encounters. These are:

- 1) Complete exstrophy of the urinary bladder.
- 2) Intractable vesicovaginal fistulas.
- 3) Certain vesical malignancies.
- 4) Extensive injuries to the urinary bladder and/or posterior urethra, which make retention of urine impossible.
- 5) Palliative diversion of the urinary stream in instances of intractable contracted urinary bladder with varying associated conditions.

We have tried many techniques for uretero-intestinal anastomosis, but it is my opinion at the present time that the most effective method of ureteral transplantation is that of Cordonnier. The immediate and overall results have definitely been better since utilizing the mucosa to mucosa and adventitia to serosa method.

I would like to present the following cases as examples:

### CASE REPORTS

*Case 1.* A 13-year-old white boy had complete exstrophy of the urinary bladder. He had never gone to school and had worn a home-devised rubber diaper since birth. His general physical condition was good and upper urinary tract studies were within normal limits. Bilateral uretero-intestinal anastomosis was carried out by the Cordonnier technique. The patient made an uneventful recovery, and several weeks later, the bladder was removed and the abdominal defect closed by a skin flap. Six months later, a plastic repair of the complete epispadias was performed and was very successful (fig. 1, A). The pyelograms at the end of a year show minimal dilatation, and the patient has had no evidence of upper urinary tract infection (fig. 1, B). He now goes to school, and for all practical purposes, enjoys good health.

*Case 2.* A 58-year-old Negress had complete urinary incontinence of 2 years' duration. It was found that she had complete destruction of the urethral sphincter and also a rectal stricture about 1½ inches above the anus (fig. 2, A). The patient was suffering from lymphopathia venereum, which had produced these conditions. Her general physical condition was good, although she had a mild dilatation

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 6, 1952.

of the right ureter. Bilateral uretero-intestinal anastomosis was carried out at one operation. She made an uneventful recovery and now stays dry from her urinary incontinence, and, in addition, at all times has a liquid stool, which is an

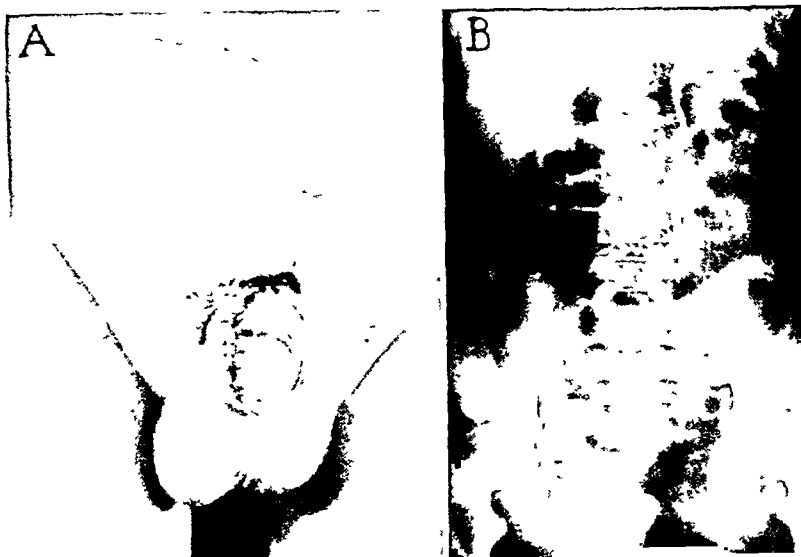


FIG. 1. *A*, repair of bladder defect by rotating skin flap and repair of epispadias. *B*, post-operative excretory urograms 1 year following ureterosigmoidostomy.



FIG. 2. *A*, complete destruction of urethral sphincter and patent urethra. *B*, postoperative excretory urogram following ureterosigmoidostomy.

aid in overcoming the rectal stricture. She does her own housework and does not get wet at night. She has had no upper urinary tract infection and has minimal dilatation of the upper urinary tract (fig. 2, *B*).

*Case 3.* A 60-year-old white man had a diagnosis made a year earlier of car-

cinoma of the bladder, which was treated then by suprapubic cystotomy and fulguration. The year prior to admission he had been hospitalized on four occasions for further fulguration. At the time of admission, cystoscopy revealed several new growths of the bladder, which biopsy proved to be transitional cell carcinoma. The patient had a bilateral uretero-intestinal anastomosis and complete cystectomy. He has had no complications, has enjoyed good health for 2 years and performs his duties as a truck farmer. He has had an occasional attack of pyelonephritis. Pyelograms at the end of one year show some dilatation of right renal pelvis and calyces (fig. 3).



Fig. 3. Excretory urogram 1 year following ureterosigmoidostomy.

*Case 4.* A 25-year-old white man had a fractured pelvis and ruptured urethra prior to admission. He had an impassable stricture in the membranous urethra and was wearing a suprapubic tube. Two unsuccessful attempts were made to excise the stricture and approximate the severed ends of the urethra. Encrustation cystitis, vesical calculi and a sinus at the penoscrotal junction developed. For all practical purposes, the patient was an invalid and was bedridden most of the time. For this reason, a bilateral uretero-intestinal anastomosis was performed. He made an uneventful recovery and at the end of 2 years was found to be working on a farm as a laborer. Excretory urograms demonstrated an almost normal upper urinary tract (fig. 4); and to the patient's knowledge, he has had no acute attacks of pyelonephritis.

*Case 5.* A 38-year-old Negro gave a history of gonorrheal infection three or four times, ten to fifteen years ago. He had no urinary difficulty until 8 years later, when he had trouble passing his urine. He was treated then for approximately 3 weeks by urethral sounds and got along fairly well until 3 months prior to ad-

mission, when his genitalia began to swell and he had marked difficulty emptying his bladder. He had some slight anemia, but his nonprotein nitrogen was within



FIG. 4. Excretory urogram at the end of 2 years following ureterosigmoidostomy

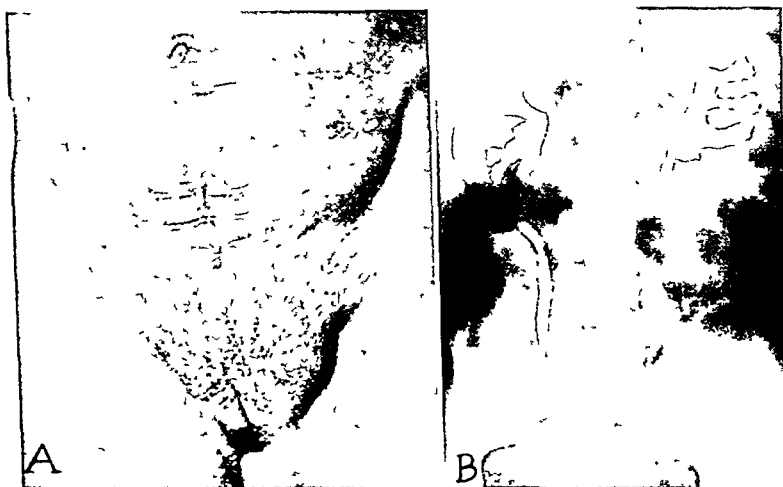


FIG 5 A, anterior view following ureterosigmoidostomy, amputation of penis, scrotum and its contents B, postoperative excretory urogram 6 weeks after ureterosigmoidostomy.

normal limits. Examination revealed a very large scrotum and penis with evidence of recent urinary extravasation and abscess formation. Other physical findings were essentially negative.

On June 21, 1949, a suprapubic cystotomy was performed with incision and

drainage of a scrotal abscess with multiple incisions in the shaft of the penis and scrotum. There was marked phimosis and when the prepuce was incised and retracted, there was an ulcerated and suspicious area on its inner aspect. A biopsy revealed a squamous cell carcinoma. The patient made an uneventful recovery, but it was still impossible to pass a filiform or other instrument through his urethra and he continued to drain purulent material through the sinuses in his perineum and scrotum. A radical amputation of the penis, scrotum and its contents was deemed advisable (fig. 5, A). This was done on July 15, 1949, followed by recovery except for some anemia, for which several transfusions of whole blood were administered. Excretory urograms demonstrated a normal upper urinary tract. Because he had had radical removal of the penis and scrotum, a



FIG. 6. Excretory urogram 6 weeks after ureterosigmoidostomy.

uretero-intestinal anastomosis was performed to dispense with the suprapubic tube. This was done on August 19, 1949. There was an uneventful recovery, and 6 weeks later excretory urograms appeared practically normal (fig. 5, B).

The patient has enjoyed good health since then and is now employed as a truck driver.

*Case 6.* A 24-year-old Negro entered the hospital because of severe dysuria and frequency. He had had this over a period of 2 years and had been hospitalized many times. Cystoscopy revealed a markedly contracted bladder and a positive culture of *Aerogenes*. He was treated with all known antibiotics and chemotherapeutic agents, but his condition grew progressively worse so that he practically lived with a urinal. Cystoscopy was carried out several times and the bladder capacity could never be increased to more than an ounce and a half. The bladder epithelium was always covered with a heavy shaggy membrane. For this reason, a bilateral uretero-intestinal anastomosis was carried out. The

patient made an uneventful recovery. Postoperative excretory urograms showed a fairly normal upper urinary tract (fig. 6). At the end of a year, he was found working as a day laborer, was asymptomatic, and had no bouts of upper urinary tract infection.

#### SUMMARY

The indications for uretero-intestinal anastomosis have been presented and examples of each given. It is believed that with present day techniques, the aid of chemotherapy, antibiotics, and lowered mortality, that we are justified in performing this procedure for a greater number of patients who in the past were considered hopeless.



drainage of a scrotal abscess with multiple incisions in the shaft of the penis and scrotum. There was marked phimosis and when the prepuce was incised and retracted, there was an ulcerated and suspicious area on its inner aspect. A biopsy revealed a squamous cell carcinoma. The patient made an uneventful recovery, but it was still impossible to pass a filiform or other instrument through his urethra and he continued to drain purulent material through the sinuses in his perineum and scrotum. A radical amputation of the penis, scrotum and its contents was deemed advisable (fig. 5, A). This was done on July 15, 1949, followed by recovery except for some anemia, for which several transfusions of whole blood were administered. Excretory urograms demonstrated a normal upper urinary tract. Because he had had radical removal of the penis and scrotum, a



FIG. 6. Excretory urogram 6 weeks after ureterosigmoidostomy.

uretero-intestinal anastomosis was performed to dispense with the suprapubic tube. This was done on August 19, 1949. There was an uneventful recovery, and 6 weeks later excretory urograms appeared practically normal (fig. 5, B).

The patient has enjoyed good health since then and is now employed as a truck driver.

*Case 6.* A 24-year-old Negro entered the hospital because of severe dysuria and frequency. He had had this over a period of 2 years and had been hospitalized many times. Cystoscopy revealed a markedly contracted bladder and a positive culture of *Aerogenes*. He was treated with all known antibiotics and chemotherapeutic agents, but his condition grew progressively worse so that he practically lived with a urinal. Cystoscopy was carried out several times and the bladder capacity could never be increased to more than an ounce to an ounce and a half. The bladder epithelium was always covered with a heavy shaggy membrane. For this reason, a bilateral uretero-intestinal anastomosis was carried out. The

patient made an uneventful recovery. Postoperative excretory urograms showed a fairly normal upper urinary tract (fig. 6). At the end of a year, he was found working as a day laborer, was asymptomatic, and had no bouts of upper urinary tract infection.

#### SUMMARY

The indications for uretero-intestinal anastomosis have been presented and examples of each given. It is believed that with present day techniques, the aid of chemotherapy, antibiotics, and lowered mortality, that we are justified in performing this procedure for a greater number of patients who in the past were considered hopeless.

## OBSERVATIONS ON NORMAL AND ABNORMAL BLADDER PHYSIOLOGY

JACK LAPIDES

*From the Department of Surgery, University Hospital, Ann Arbor, Mich.*

Despite the numerous reports of investigations dealing with bladder function and the gradual evolvement of a factual concept of micturition, misunderstandings exist relative to the diagnosis and treatment of many functional disorders of the bladder. In this paper an attempt will be made to present several of the known facts about bladder physiology, the experimental and clinical evidence for the facts and the application of this knowledge in the diagnosis and treatment of vesical dysfunctions.

### SECTION I. BLADDER TONUS AND CAPACITY

Tonicity of the smooth muscle of the bladder and its true capacity are dependent upon the intrinsic properties of smooth muscle and not upon the central nervous system. Traumatic as well as chemical blockade of nervous impulses from the central nervous system produces no change in bladder tonicity or capacity. The blockade of the parasympathetic pathways, however, does result in abolition of the voiding contraction of the bladder.

*A. Experimental observations.* Cystometry was used in evaluating bladder function; a standardized method<sup>1</sup> and a simplified cystometer<sup>2</sup> were employed. Procaine spinal anesthesia, Etamon and Banthine<sup>3</sup> were administered in order to produce a blockade of motor impulses to the bladder. Spinal anesthesia blocks all sensory and motor impulse in that portion of the spinal cord affected by the procaine. Etamon, a quarternary ammonium salt, blocks the transmission of all motor impulses at the autonomic ganglia, both sympathetic and parasympathetic. Banthine, also a quarternary ammonium derivative, not only blocks motor impulses at the autonomic ganglia but in addition has a blocking effect at the endings of postganglionic cholinergic nerves, i.e., an atropine-like action. Five patients were subjected to spinal anesthesia, sixteen were given Etamon (500 mg. i.v.) and fifteen were administered intravenous Banthine (150-200 mg.). All of the patients demonstrated normal bladders on cystometric examination prior to drug administration. Following spinal anesthesia and intravenous injection of Etamon and Banthine, cystometric examination was repeated and it was observed that bladder capacity and tonicity were unchanged but the patients were unable to void. Figure 1 illustrates cystometrograms typical of all the patients

George L. McKesson Fellow

Banthine supplied through courtesy of G. D. Searle & Company.

This study was supported in part by a research grant from G. D. Searle & Company.

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 4, 1952.

<sup>1</sup> Nesbit, R. M. and Lapides, J.: Tonus of the bladder during spinal "shock." *Arch. Surg.*, 56: 139-44, 1948.

<sup>2</sup> Nesbit, R. M.: Fundamentals of Urology. Ann Arbor; J. E. Edwards, 1948.

<sup>3</sup> Lapides, J. and Dodson, A. I., Jr.: Preliminary report: A study of the effects of banthine on the human bladder. *J. Urol.*, 69: 96-101, 1953.

before and after chemical blockade of motor impulses. Figure 1, *A* depicts a normal bladder before chemical blockade and figure 1, *B*, the unchanged bladder capacity and tonicity (but with absence of a voluntary voiding contraction) after blockade.

*B. Clinical observations.* Bladder capacity and tonicity were determined by cystometric examination on 8 patients in spinal shock; these patients were examined within several hours after spinal cord injury. All of the patients exhibited a flaccid paralysis of the skeletal muscle below the level of the spinal injury but in no case was an atonic, flaccid bladder observed. In figure 2 can be observed the cystometrograph of one of these patients. Note that bladder tonicity and capacity are within normal limits.

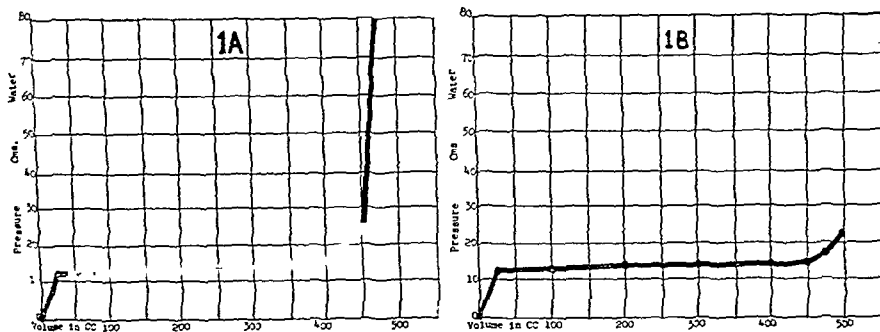


FIG. 1

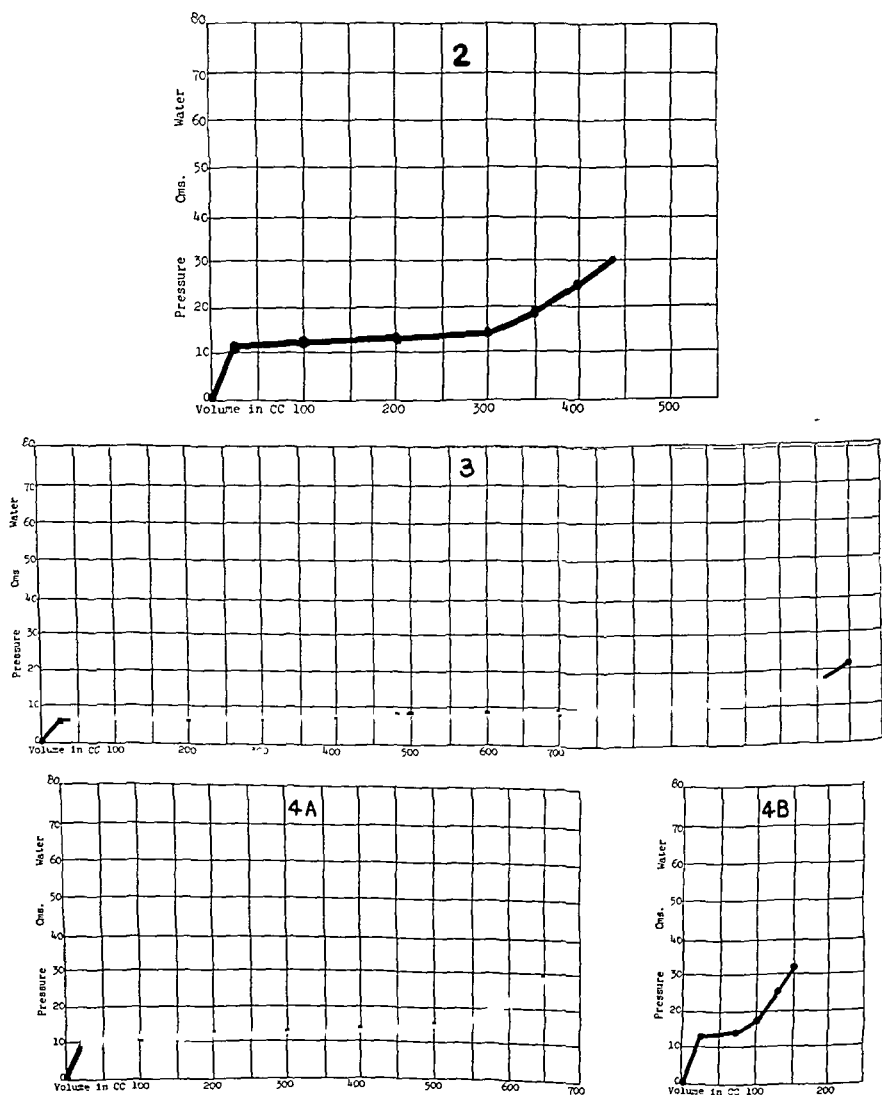
Atonic, large-capacity bladders were observed in spinal-shock patients who had not been catheterized for days following injury and had been allowed to develop overflow incontinence. Similar atonic bladders have been noted in patients with *chronic urinary retention* due to urethral strictures or prostatic obstruction. Figure 3 illustrates the cystometrograph of a patient with such an atonic bladder.

Small capacity, hypertonic bladders have been seen in patients who have been on dependent continuous bladder drainage for a prolonged period of time. Figure 4, *A* is the cystometrograph of a patient in whom acute urinary retention developed; he was placed on suprapubic cystostomy because a definitive prostatectomy could not be performed for several months due to malnutrition and cardiac disease. The patient remained at home for several months on continuous dependent drainage of the bladder. When he returned to the hospital, cystometric examination disclosed a small-capacity, hypertonic bladder (fig. 4, *B*). This phenomenon has been observed repeatedly in many patients under similar circumstances.

*C. Therapeutic implications.* On the basis of the data presented, it is readily apparent that bladder tonus is an inherent property of vesical smooth muscle and is independent of its extrinsic motor supply. Atonicity is caused only by prolonged stretching of bladder muscle due to retention of large amounts of urine. Similarly small-capacity bladders obtain when the bladder is kept empty over a period of time by continuous drainage or marked frequency of urination.

It is thus evident that spinal-shock patients should be catheterized as soon as possible and their bladder capacities kept within normal limits by appropriate measures; some clinicians advocate tidal drainage for this purpose. A simple and

more efficacious procedure is to fill the bladder to 250–350 cc volume and keep it filled for one-half hour, two or three times a day; this is, in effect, the method by which the average individual maintains normal bladder capacity.



FIGS. 2, 3, 4

Another application of the principle of tonicity can be observed in the treatment of patients with sensory paralytic bladders due to tabes dorsalis. In these patients luetic involvement of the nervous system results in an insidious loss of the sensation of fullness or distention of the urinary bladder. Because of this gradual loss of proprioceptive sensation, the patient's bladder must be filled with greater and greater amounts of urine before he is aware of a desire to urinate,

with the result that overdistention of the bladder occurs with the development of atonicity and incomplete emptying. In the early stages this condition can be corrected by requiring the patient to void every two to three hours (during the day) by the clock instead of relying upon his sensation of fullness. In far-advanced stages it is necessary to place the patient upon continuous bladder drainage by catheter for a prolonged period of time before tonicity will be regained. Occasionally tonicity is never regained because of the permanent damage incurred by the bladder muscle.

As has been stated previously, large atonic bladders are sometimes seen in patients with chronic urinary retention due to prostatism. In these patients the removal of obstructing prostatic tissue with the establishment of an adequate channel will not be followed by complete emptying of the bladder. The contraction of the decompensated bladder is too feeble to overcome normal urethral resistance. These patients should be placed on prolonged suprapubic catheter drainage and frequent cystometric examinations made in order to determine when bladder tonicity is regained. When bladder tonicity becomes adequate, then a prostatectomy will result in complete emptying of the bladder.

Permanent bladder drainage may be necessary for the occasional bladder which never regains tonicity. Partial resection of the bladder<sup>4</sup> has been advocated as another therapeutic measure in the treatment of the permanently atonic bladder. This procedure will reduce residual urine markedly by decreasing bladder capacity. However, in our experience, this operation does not reduce residual urine to within normal limits.

## SECTION II. THE UNINHIBITED NEUROGENIC BLADDER

In the practice of urology, one often encounters patients with symptoms of increased frequency of urination, urgency, precipitate micturition, nocturia and enuresis. Many of these patients, after routine examination, are found to have sterile urine and apparent normal genito-urinary tracts. The cause for the urinary symptoms will not be found until a cystometric examination is made. In some of these individuals the bladder will exhibit numerous uncontrolled contractions while filling with fluid. Figure 5, *A* demonstrates the cystometrograph of one of these patients as compared with the cystometrograph (fig. 5, *B*) of a normal bladder. It will be seen that the normal bladder maintains a smooth curve as it is distended while the abnormal bladder exhibits sharp contractions with a final uncontrolled voiding contraction. These patients have normal superficial and deep sensation, and can empty their bladders completely. They can usually initiate micturition at will but have varying degrees of difficulty inhibiting urination.

The ineffectiveness in controlling micturition is due to a lesion of the cortical regulating tract or to a defect in integration in the higher centers. As is well known, the individual controls his voluntary muscular activity through the pyramidal tracts. Hyperactive knee jerks, ankle clonus, positive Babinski and Hoffman signs are manifestations of a lesion of the pyramidal tract or defective

<sup>4</sup>Crabtree, E. G. and Muellner, R. S.: The bladder in prostatism: An operation for excessive bladder hypertrophy. *J. Urol.*, 60: 593-598, 1948.

voluntary control. The bladder too reflects evidence of defective voluntary control by the symptoms of increased frequency of urination, urgency, precipitate micturition, and incontinence. This type of micturitional behavior is often seen in multiple sclerosis, brain tumors, injuries of the spinal cord and cerebrovascular accidents. The same symptoms are sometimes observed in psychoneurotics but in that group the cystometric study is normal.

One observes lack of control of micturition in the infant or young child. In this instance, the defective control is due to incomplete development of cerebral integration and not to a lesion of the cortical regulating tract. In most individuals complete integration and normal voluntary control are attained at the age of 3-5 years but there are a considerable number of people who never develop fully in this respect; and it is in these individuals that cystometric examination is necessary for diagnosis, for they do not exhibit hyperactive reflexes, ankle clonus or Babinski signs.

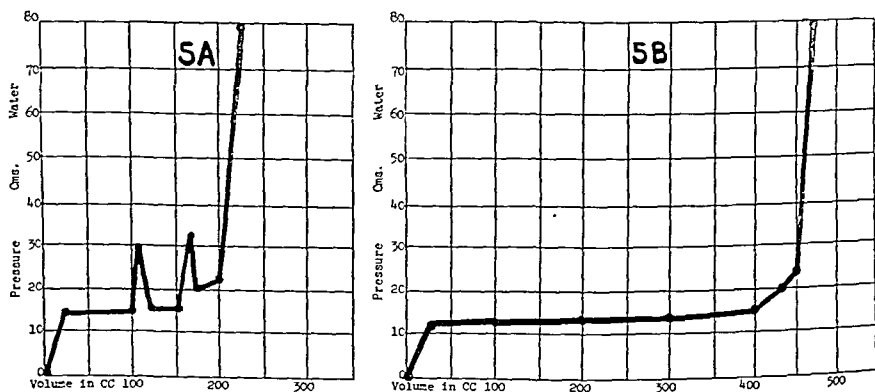


FIG. 5

*A. Experimental observations.* Forty-five patients who were found to have uninhibited neurogenic bladders on cystometric examination were selected as subjects. In the first portion of the study procaine spinal anesthesia (100 mg.) was administered to 5 patients, Etamon (500 mg. i.v.) to 10 patients and Banthine (200 mg. i.v.) to 20 patients. Cystometrographs were performed prior to and following drug administration as previously described.

Figure 6, A indicates the typical cystometrograph of a patient with an uninhibited neurogenic bladder. In figure 6, B can be observed the characteristic response of this type of bladder to blockade of the parasympathetic motor pathways. Note that the uncontrolled contractions have been abolished, apparent bladder capacity is increased and micturition is completely abolished. Spinal anesthesia produces absence of all bladder sensation while Etamon and Banthine have no effect on the sensory fibers.

In the second portion of the study ten patients with uninhibited neurogenic bladders were given Banthine, 50-100 mg. orally q.i.d. for a period of 5 days. This dosage will depress but not completely inhibit the motor impulses to the bladder. Cystometric examinations were conducted prior to drug administration,

three days after start of Banthine therapy and three days following cessation of medication. Figure 7, *A* is the pre-Banthine cystometrograph of one of these patients. Symptomatically all of the patients showed marked improvement after several days of Banthine therapy; frequency of urination became normal, precipitate micturition and incontinence had disappeared. Cystometric examination (fig. 7, *B*) reveals absence of uncontrolled contractions of the bladder and increased apparent bladder capacity with persistence of normal sensation and ability to empty the bladder completely. Three days after discontinuing Banthine original symptoms recurred and the cystometrograph (fig. 7, *C*) again showed involuntary voiding contractions of the bladder.

Five patients with symptoms of increased frequency of urination and enuresis but with normal cystometrographs, were given 100 mg. of Banthine orally 4 times a day for 3 days. The symptoms of these patients were not relieved by Banthine and their cystometrographs were unchanged after three days of therapy. Figure 8, *A* is the pre-Banthine cystometrograph and figure 8, *B* is the unchanged cystometrograph during Banthine therapy. In these cases the symptoms were doubtless psychoneurotic and not neurogenic, therefore not responsive to drug therapy.

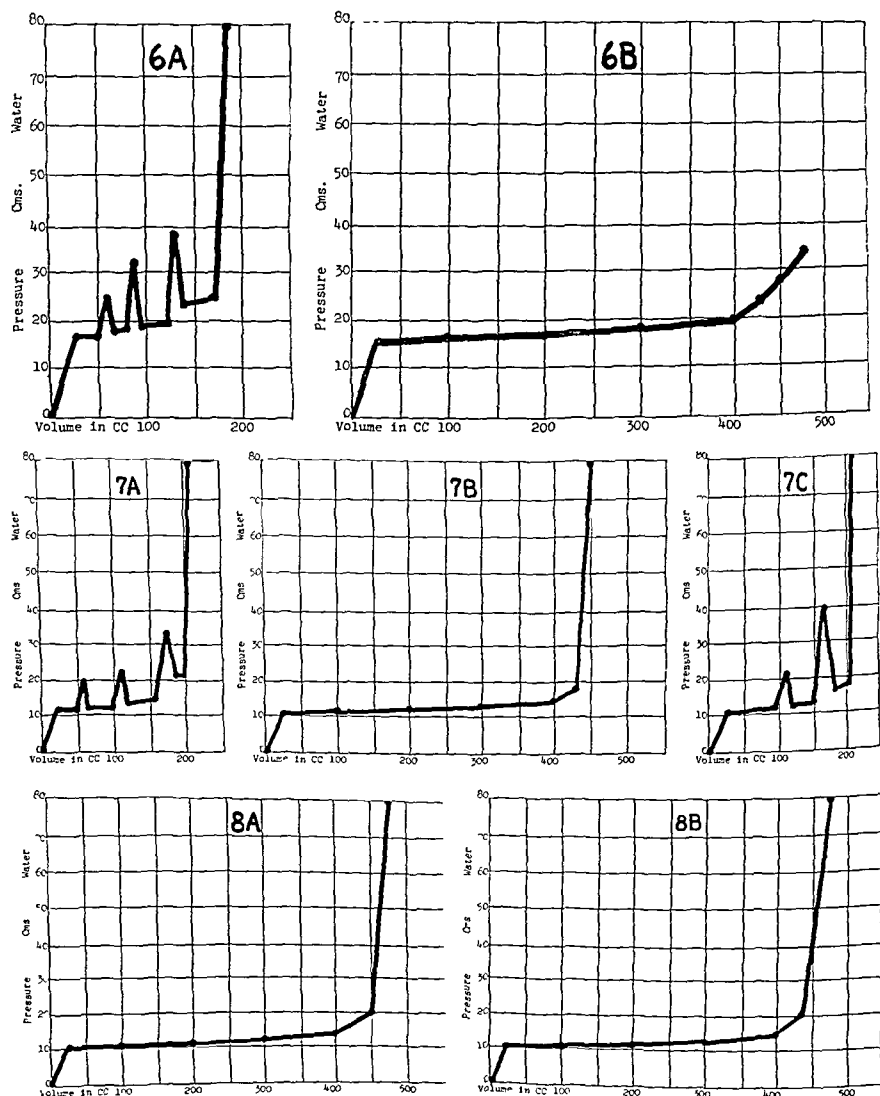
*B. Clinical observations.* Cystometrographs were made on patients with known lesions of the pyramidal tract. Eight patients had suffered cerebrovascular accidents; ten were diagnosed as multiple sclerosis; six were found to have luetic paresis; three had tumors of the spinal cord; two patients had cerebral palsy and four had undergone cordotomies. All of these patients exhibited varying degrees of hyperactivity of the ankle and knee jerks and positive Babinski signs. Some of the patients also demonstrated ankle clonus. The patients who were well oriented complained of increased frequency of urination, urgency, precipitate micturition and enuresis. The cystometrographs uniformly revealed uncontrolled or uninhibited voiding contractions of the bladder.

*C. Therapeutic implications.* From the data presented it is apparent that there is a group of patients who have severe urinary tract symptoms not related to infection, stones, neoplasm, stricture, prostatism or urethrocystitis. Their symptoms are due entirely to a defect in cerebral integration or to lesions of the cortical regulating tracts which result in the failure of proper inhibition or control of micturition.

The spinal pathways and the local reflex arc concerned with urination are illustrated in figure 9. In the normal individual, as the bladder fills with urine and is stretched, stretch receptors in the bladder wall are stimulated to give rise to sensory impulses which are conducted along sensory fibers to the spinal cord. In the spinal cord the sensory impulses impinge upon the motor neurones of the bladder (located at the level of sacral spinal segments 2, 3 and 4) and also are conducted to the higher centers along the ascending sensory tracts. The motor neurones do not respond to the sensory impulses until the individual voluntarily desires to void. The cortical regulating tract which has endings around the lower motor neurones prevents the firing of the motor neurones until the higher center releases its inhibitory effect. In patients with the uninhibited neurogenic



bladder the lower motor neurones are not effectively inhibited because of a lesion of the cortical regulating tracts and, thus, as the bladder is moderately distended, sensory impulses impinge upon the motor neurones and activate some of them to send motor impulses to the bladder and cause its contraction.



FIGS. 6, 7, 8

The uninhibited neurogenic bladder can be brought under satisfactory control by the use of moderate doses of oral Banthine. Banthine blocks the pathway of the motor impulses at the parasympathetic ganglion and at the postganglionic cholinergic endings (fig. 9). The dosage of Banthine used should be enough to block the uncontrolled discharge of the motor neurones but not enough to stop

the barrage of motor impulses discharged voluntarily. In other words the dose of Banthine should be large enough to prevent increased frequency of urination, precipitate micturition and incontinence but small enough to permit the patient to empty the bladder voluntarily without residual urine. The usual dose for this level of activity is 50-150 mg. Banthine orally q.i.d.

It should be emphasized that patients with enuresis and increased frequency of urination who have normal cystometrographs will not be helped by Banthine.

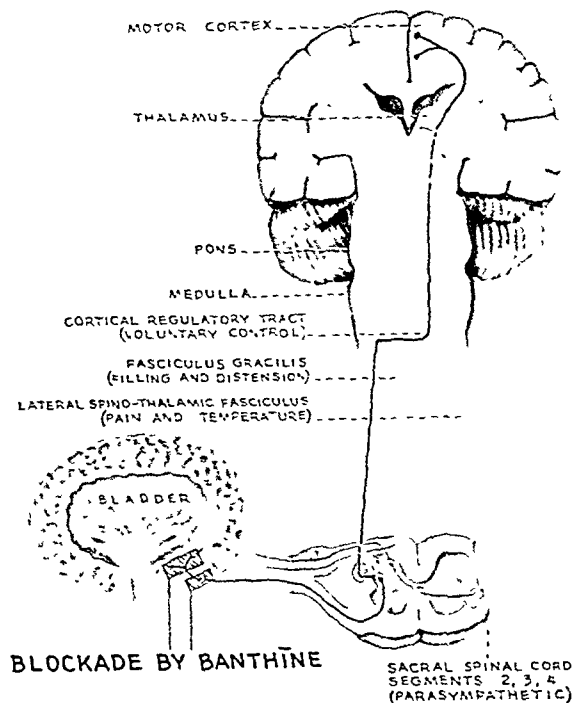


FIG. 9

### SECTION III. BLADDER FUNCTION IN SACRAL SPINAL CORD LESIONS

The sensory and motor neurones associated with bladder function are located in sacral spinal cord segments 2, 3 and 4 (fig. 9). When a disease process involves the spinal cord at this level, the neurones cease functioning and the bladder becomes an inert structure, i.e., disappearance of all bladder sensation and absence of any voiding contractions; the patient develops urinary retention with overflow. Sectioning both pelvic nerves produces the same effects.

A. *Experimental observations.* Five patients with normal bladder function were administered low spinal anesthesia in order to abolish activity of the sensory and motor neurones supplying the bladder. Cystometrographs were obtained before and after spinal anesthesia. In all patients, following spinal administration of procaine, bladder sensation was abolished and the patients could not void except by overflow. Bladder tonicity and capacity were unchanged.

B. *Clinical observations.* Cystometric examinations were conducted on patients with apparent lesions of the sacral spinal cord. The diagnoses made in these subjects were spina bifida, myelomeningocele, gunshot wound, primary neoplasm of the spinal cord and metastatic neoplasm of the cord. Some of the patients demonstrated complete loss of sensation and urinary retention. Others exhibited varying degrees of sensory loss as well as decreased strength of the voiding contraction of the detrusor. All of the patients showed some degree of saddle anesthesia. The level of involvement of the spinal cord in those patients with tumors and gunshot wounds was confirmed at operation.

C. *Clinical significance.* Since frequently the first symptom of a sacral spinal cord lesion is urinary retention, it is not uncommon for the urologist to see these patients initially. A very striking example of the value of the cystometric examination in diagnosing the sacral spinal cord lesion is the case history of a 24 year old man who was admitted to the hospital with the chief complaint of difficulty in urination. The patient, of rather limited intelligence, stated that for 3 months prior to admission to the hospital he had noticed increasing difficulty in emptying his bladder. His past history revealed that the left testis had been removed several years prior for a reason not known by the patient. Physical examination was essentially negative except for absence of the left testis. Urinalysis and blood examination revealed no abnormalities. A cystometric examination was performed with the following findings: 1) complete absence of all bladder sensation, 2) residual urine of 600 cc, 3) absence of any voiding contraction. The cystometric examination thus suggested a lesion involving both the motor and sensory limbs of the bladder reflex arc. This type of lesion can be found in only one region, namely, the sacral spinal cord. A neurological examination revealed anesthesia of the perineal region, an area whose sensory neurones lie at the level of the sacral spinal cord. A tentative diagnosis of metastatic testicular neoplasm involving the sacral spinal cord was made. One week later an exploratory laminectomy revealed metastatic invasion of the sacral spinal cord by seminoma.

The cystometric examination will also aid in defining the cause for persistent urinary retention in postoperative combined abdomino-perineal resections. Most of the patients develop urinary retention because they are borderline prostatics preoperatively and are on the verge of decompensation of the bladder. The operative procedure is sufficient to throw them into retention. Prostatectomy relieves this situation very adequately. In a small percentage of patients, however, the pelvic nerves are sectioned or injured. Cystometry, in these individuals, will reveal lack of sensation and absence of a voiding contraction of the bladder. In these patients the reflex arc has been interrupted both on the sensory and motor side, since the sensory and motor fibers of the bladder are carried in the pelvic nerve.

The treatment of patients with urinary retention due to sacral cord lesions or pelvic nerve injury will vary with the etiology of the lesion. If the lesion is due to an incurable neoplasm which is expected to eventually result in death, it is best to place the patient on suprapubic or perineal urethrostomy bladder drainage.

If the lesion is static as it may be in myelomeningocele, spina bifida, gunshot

wound or trauma, one advises the patient to void by abdominal straining and the use of the Credé maneuver. Transurethral resection of the vesical neck may be especially efficacious in improving function in this type of neurogenic bladder. It should be emphasized that the type of bladder described in this section is incapable of any voiding contraction, either voluntary or involuntary. All evacuation must be accomplished by external pressure upon the bladder, either through abdominal straining or by manual pressure.

#### SUMMARY

Experimental and clinical evidence for some of the known facts about bladder physiology have been presented. An attempt has been made to indicate the rational application of this knowledge in the diagnosis and treatment of bladder dysfunctions.

## MALACOPLAKIA OF THE URINARY TRACT: REPORT OF THREE CASES

WILLIAM H. BENNETT

*From the Department of Pathology and Urology, Emory University School of Medicine and Grady Memorial Hospital, Atlanta, Ga.*

Malacoplakia is a rare lesion of the urinary tract. It most frequently involves the bladder but has been observed to involve the urethra, ureters, renal pelvis and renal parenchyma. When seen at cystoscopic examination, the nodules appear in the bladder or urethra as yellowish-gray or brownish elevations of the mucosa, with or without central umbilication. The lesion is identified microscopically by the presence of large phagocytic cells containing Michaelis-Gutmann bodies which are thought to be deposits of calcium and iron.

The disease is more common in women, usually in the middle age group. The symptoms are grossly those of cystitis, but diagnosis can be made only on biopsy of the lesion. If the lesions occur where they cannot be demonstrated by cystoscopy and confirmed by biopsy, there are no means at present whereby the diagnosis can be established. Clinically, the lesion must be differentiated from neoplasms for the presenting symptoms and gross appearance are often quite similar.

There is an unexplained relationship between urinary tract infection and malacoplakia because infection in the upper urinary tract or bladder has been demonstrated in almost all cases reported and furthermore, cure of the primary urinary tract infection has been shown to cause disappearance of the lesion of malacoplakia.

Malacoplakia was first described in 1902 and recognized by cystoscopy in 1918. Modern urologic investigation is probably responsible for the increasing frequency with which the lesion is now found.

The purpose of this paper is to report three additional cases, discuss the etiology, and present additional etiological factors. One of these cases is unusual in that the characteristic nodules were not demonstrable in the bladder mucosa. An area of the bladder wall which had the appearance of local inflammation proved on histologic examination to be malacoplakia. Presuming that this represented a preclinical state in the development of a malacoplakia nodule, bladder sections taken at necropsy from 232 cases of cystitis were reviewed in an attempt to discover additional information concerning the etiology.

### REPORT OF CASES

*Case 1.* L. J. B., a female Negro, aged 40, was admitted to Grady Memorial Hospital on May 2, 1945, because of dull pain in the right flank of four weeks' duration. Other symptoms were increasing epigastric distress, weakness and dyspnea. The patient denied all symptoms of urinary tract disease. She had received inadequate treatment for syphilis four years previously.

Physical examination revealed a poorly nourished, pale, weak, dehydrated

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 6, 1952.

woman who was critically ill. Blood pressure was 130/50, temperature 98.6F, pulse rate 100 per minute. Principal physical findings, other than generalized arterio-sclerosis, were confined to the abdomen where a firm, slightly tender mass was found almost entirely filling the right abdomen, and a smaller, firm, non-tender mass in the left upper quadrant.

Laboratory data: Urinalysis: pH 6.0, specific gravity 1.012, albumin strongly positive, sugar negative, many red blood cells, innumerable pus cells and many epithelial cells. A culture grew *Escherichia coli*. Phenol-sulphonphthalein test showed 15 per cent return in two hours.

Blood count: Erythrocytes 1.4 million, hemoglobin 3.8 Gm. (Klett), leukocytes 30,200 with 85 segmented cells and 15 lymphocytes. Blood nonprotein nitrogen was 188 mg. per cent.

Cystoscopic examination revealed several small yellowish-brown, slightly elevated nodules in the bladder mucosa about the trigone. The largest nodule was approximately 1 cm. in diameter. Elsewhere the bladder was hyperemic or edematous. Biopsy specimens were taken from the larger nodules for histologic study, using cystoscopic rongeur forceps. Retrograde pyelograms showed bilateral polycystic kidney disease.

Biopsy report: The sections showed fragments of tissue covered in part on one surface by transitional cell epithelium which was sometime thinned out and displayed occasional slight infiltration by neutrophilic polymorphonuclear leukocytes. The tissue beneath the epithelium was taken up by densely packed masses of large, pale-staining cells without any architectural pattern. The cells were quite uniform in size and the dimensions were approximately those of a large mononuclear cell. Their nuclei were eccentrically placed. They displayed some variations ranging from large, vesicular and oval with a prominent nucleolus to small, dense and lobate without discernible nuclear architecture. Occasional binucleated cells could be found (fig. 1).

The cytoplasm was ample with well-defined contours. In general, it appeared finely and rather evenly granular and stained acidophilic with the phloxine-methylene blue stain. Inclusion bodies were found in a fair proportion of these cells. These inclusions were basophilic and varied in size, sometimes taking up only small portions of the cytoplasm while in other instances masses of them appeared to occupy the entire cell. The smaller ones varied from round to elongated while larger aggregates displayed an irregular shape.

Occasionally, structures similar to the inclusion bodies could be found free in the tissues, generally in the vicinity of degenerating cells of the type described above. In those areas a slight to moderate infiltration of polymorphonuclear leukocytes was noted.

Small numbers of plasma cells and lymphocytes were occasionally seen. These cells tended to accumulate around the thinly-walled vessels which were present in fair numbers throughout the tissues. Some of these vessels were rather congested and a few displayed leukocytic margination as well as infiltration. A delicate connective tissue framework was present.

Intensive general supportive therapy was unsuccessful. The patient died on

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short duration, but she denied all other symptoms of urinary tract disease. Two negative urinalyses were recorded during the 2 years prior to admission.

Physical examination revealed a well nourished female who was in a deep coma. The respiration was of Cheyne-Stokes type. The blood pressure was 210/110, temperature 100.2F, pulse rate 96 per minute, and respirations roughly 30 per minute. Advanced arteriosclerotic changes were seen in the fundi. There was marked cardiac enlargement with an apical friction rub and severe, generalized pitting edema.

Laboratory data: Urinalysis: pH 7.5, specific gravity 1.008, albumin strongly positive, sugar negative, innumerable red blood cells, pus cells and epithelial cells. The stained sediment revealed many gram-negative rod-shaped bacilli. Cultures grew *Escherichia coli* on two occasions. A tiny fragment of material found in the urine was examined microscopically and found to consist of blood clot, purulent exudate, and masses of microorganisms.

Forty-eight hours after admission the patient died in acute cardiorenal failure.

Necropsy report: The clinical impression of the illness was confirmed at necropsy. On examination of the urinary bladder, an area of edema and hyperemia approximately 3 cm. in diameter was noted in the area posterior to and above the trigone.

Microscopic examination: Sections of the bladder displayed an intact although occasionally slightly thinned out epithelium. The lamina propria was edematous and the layer immediately below the epithelium showed ill-defined focal areas of cellular infiltration. This infiltration consisted in general of lymphocytes and plasma cells, but in some areas collections of large cells were found. These cells, although less densely packed, corresponded in every detail to the cells described in the first case (fig. 2). Deeper layers of the bladder wall, including the muscularis, showed nothing of note.

Sections of the renal pelvis and ureters revealed only a slight degree of chronic inflammation without evidence of malacoplakia.

*Case 3.* Mrs. G. C., white, aged 82, was admitted to the medical service of Grady Memorial Hospital on March 24, 1948, with a diagnosis of pulmonary fibrosis with patchy pneumonitis. The history was irrelevant except for symptoms of frequency, urgency, and burning on urination in recent months. There was no history of hematuria or pyuria. A local doctor had treated her for "bladder infection" on many occasions during the past five years, but the patient's bladder had not been examined, nor had an upper urinary tract examination been made.

Physical examination revealed an acutely ill, old woman who was dyspneic and orthopneic. Blood pressure was 130/118, pulse 100 with many extrasystoles, and respiration 34 per minute. Numerous fine crackling rales were heard over both lung bases. The heart was enlarged with a harsh, systolic murmur heard all over the precordium and a corresponding systolic thrill over the same area. There was a faint diastolic murmur over the aortic area. There was moderate tenderness in the epigastric area, but no masses could be palpated in the abdomen.

Laboratory data: Urinalysis: pH 8.0, specific gravity 1.014, trace of albumin,



the tenth hospital day from acute renal failure. Necropsy permission was not granted.

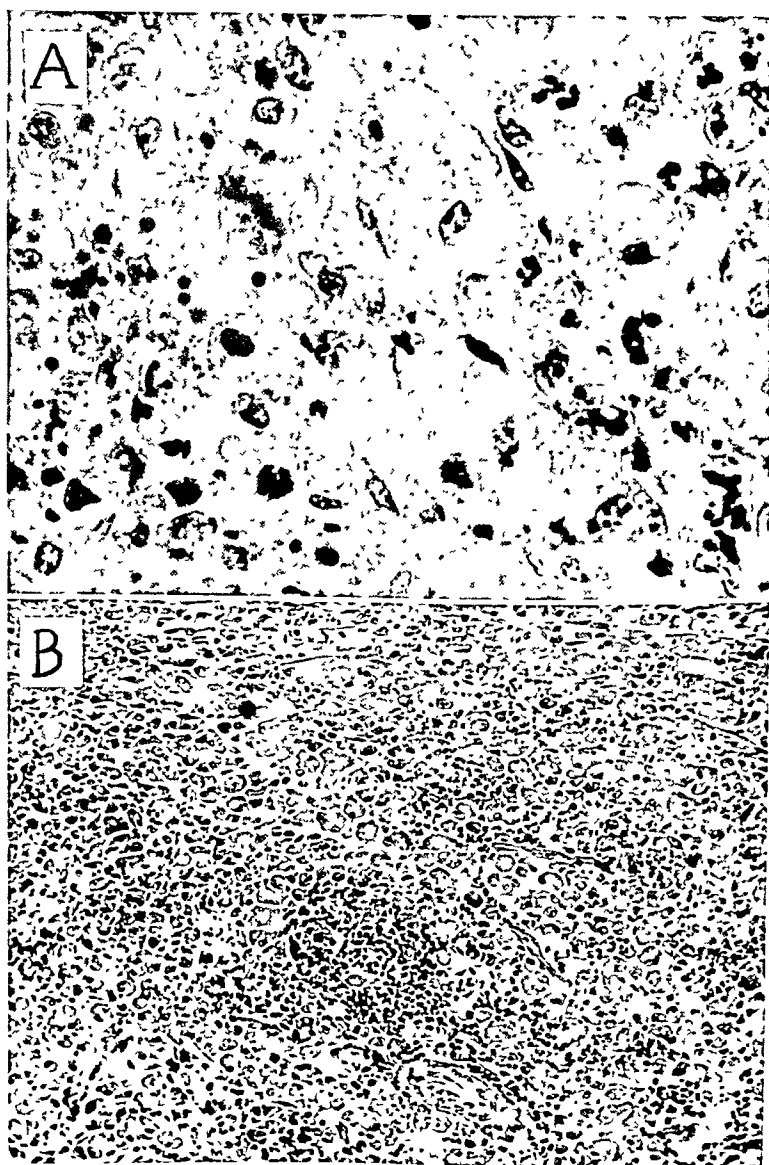


FIG. 1. Case 1. *A*, section of bladder showing large polyhedral cells with Michaelis-Gutmann inclusion bodies (PMB stain  $\times 175$ ). *B*, center section of *A* (PMB stain  $\times 660$ ).

*Case 2.* B. B., a female Negro, aged 39, was admitted to Grady Memorial Hospital on August 18, 1947, in acute cardiorenal failure. From the outpatient clinic record it was noted that this patient had had hypertensive heart disease for 3 years and that 3 months prior to this admission, she had had hematuria of

malacoplakia has been associated with a urinary tract infection.<sup>3, 4, 5, 6, 7, 8</sup> In many cases reported, histories suggestive of cystitis have been described.<sup>9, 10, 11, 12</sup>

Because of the rarity of the disease and the lack of experimental study, the etiology remains obscure although many explanations have been offered. Kimla<sup>13</sup> suggested tuberculosis as a factor, but it is now believed to be a coincidental finding. McDonald and Sewell,<sup>6</sup> who found the lesions in the renal pelvis, suggested that they were embryonal cell rests activated by bacterial invasion. Dickson, Gray and Kidd<sup>4</sup> found mycotic parasites in their specimens and thought the Michaelis-Gutmann bodies represented parasites. Gierke and Loele<sup>59, 14</sup> believed that urine precipitates were formed in the submucosa by bacterial action on mineral salts contained in urine. Redewill<sup>15</sup> pointed out the similarity of malacoplakia and sarcoidosis.

The purpose of this study was to show, if possible, how malacoplakia develops. As was mentioned previously, one of the cases presented here (case 2), fulfilled the microscopic characteristics but not the gross appearance. Cases for further study were selected which fulfilled these requirements: 1) They had a clinical

TABLE 1. Study of bladder sections taken at necropsy in 232 cases of urinary tract infection

|                                         | MALE | FEMALE | TOTAL |
|-----------------------------------------|------|--------|-------|
| Upper and lower urinary tract infection | 73   | 91     | 164   |
| Bladder calculi                         | 12   | 2      | 14    |
| Retention catheters, 14 days duration   | 9    | 3      | 12    |
| Cystitis other than above               | 14   | 20     | 34    |
| Tuberculosis involving urinary tract    | 6    | 2      | 8     |
| Total cases examined                    | 114  | 118    | 232   |

history of cystitis and a urinalysis showing innumerable pus cells and 2) the necropsy sections of the urinary tract tissues were available for study. Two hundred thirty-two cases were selected (table 1).

There were 164 cases of upper and lower urinary tract disease. Fourteen cases had calculi present in the bladder cavity ranging in size from a single stone  $1\frac{1}{2}$  cm. in diameter to four stones, the largest of which was 5 cm. in diameter. Twelve cases had been treated by continuous catheter drainage for more than 14 days

<sup>3</sup> Cristol, D. S. and Broders, A. C.: *J. Urol.*, 55: 260-266, 1946.

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<sup>5</sup> Gierke, E.: *Muenchen med. Wehnschr.*, 52: 1388-1389, 1905, cited by Cristol.<sup>3</sup>

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<sup>7</sup> Morison, J. E.: *J. Path. & Bact.*, 56: 67, 1943.

<sup>8</sup> Papenheimer, A. M.: *Proc. New York Path. Soc.*, 1906, pp. 65-71.

<sup>9</sup> McCrae, L. E.: *Clinical Cystoscopy*. Philadelphia: F. A. Davis Co., 1946.

<sup>10</sup> Chisholm, A. E. and Tudhope, G. R.: *Edinburgh Med. J.*, 41: 626-629, 1934.

<sup>11</sup> Folsom, A. I.: *J.A.M.A.*, 73: 1112-1114, 1919.

<sup>12</sup> Thomson-Walker, J. and Barrington, F. J. F.: *Proc. Roy. Soc. Med.*, 16: 32-34, 1923

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sugar negative, many small clumps of pus cells and many epithelial cells. Culture was not made.

Blood count: Erythrocytes 4.0 million, hemoglobin 11.5 gm. (Klett), leukocytes 14,500 with 78 segmental cells and 22 lymphocytes. Blood nonprotein nitrogen was 59 mg. per cent. There was no growth on three blood cultures.

The patient died 17 hours after admission.

Necropsy revealed the primary cause of death to be bronchopneumonia. Cystitis cystica was noted in generalized distribution on the bladder mucosa, more extensive in the area of the trigone. The kidneys revealed ulceration of the very tips of many of the renal papillae. The papillae were sharply defined and were yellowish-brown in color. Histologic examination of section from the renal

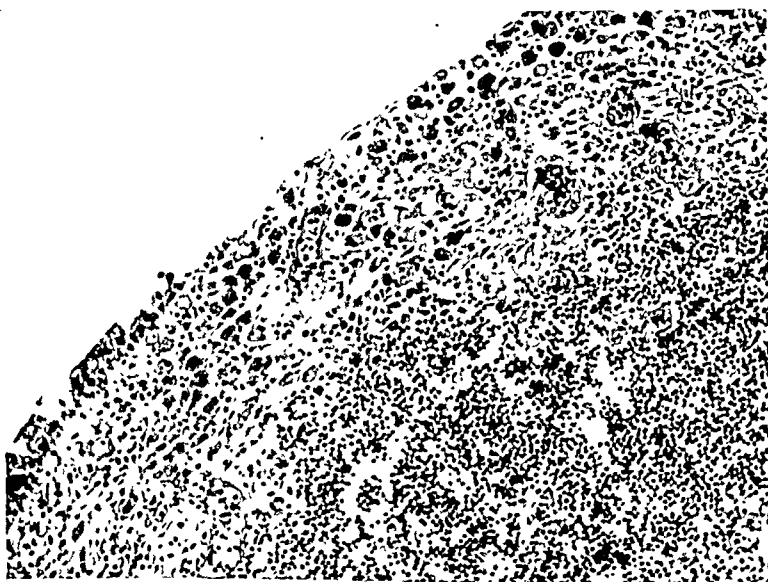


FIG. 2, Case 2. Section of bladder showing essentially the same pathological changes noted in fig. 1, A.

papillae showed a picture of malacoplakia similar to that described in the preceding cases. Histologic examination of the other structures of the urinary tract showed no significant lesions.

#### DISCUSSION

Malacoplakia was first described by Michaelis and Gutmann<sup>1</sup> (1902) and was named a year later by von Hansemann.<sup>2</sup> Michaelis and Gutmann considered the lesions to be neoplastic. Von Hansemann noted the presence of gram-negative bacteria but did not think them significant. In the majority of cases reported,

<sup>1</sup> Michaelis and Gutmann: *Ztschr. f. klin. Med.*, 47: 208, 1902, cited by McDonald and Sewell.<sup>6</sup>

<sup>2</sup> Von Hansemann: *Virchow's Arch. f. path. Anat.*, 173: 302, 1903, cited by McDonald and Sewell.<sup>6</sup>

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prior to death. There were 8 cases of urinary tract tuberculosis. The other 34 cases had cystitis of miscellaneous types.

One hundred seventy-nine cases, or 79 per cent, had positive urine cultures and 65 per cent of cultures were *Escherichia coli*.

The microscopic picture in all of the cases studied showed cellular infiltration into the mucosa, submucosa or muscularis of the bladder wall. Several of the sections showed a few large multi- or mononucleated cells in the submucosa, but none of these cells had the characteristics of the large phagocytic cells of malacoplakia. Those cases in which *B. coli* was the causative organism had no significant differences in the microscopic picture.

Calculi in the bladder caused a heavier accumulation of polymorphonuclear cells but not an increase in the number of large phagocytic cells. These same findings were true in the cases treated by retention catheters.

The sections from patients with tuberculosis were searched very carefully. Michaelis-Gutmann bodies were not found.

The presence of arteriosclerotic vessels in the bladder wall of the reported cases led to further search for malacoplakia cells in the 232 cases studied here. Marked arterial disease was occasionally noted, but these sections did not have an increase in the number of large phagocytic cells and Michaelis-Gutmann bodies were not found.

It would appear, therefore, that the usual diseases of the urinary bladder are not associated with malacoplakia. Trauma to the mucosa, caused by calculi or foreign bodies, is probably not an etiological factor. The severity of infection is of no significance.

#### SUMMARY AND CONCLUSIONS

Three additional cases of malacoplakia are reported. Two are typical; the other is of interest because nodule formation was not apparent.

Microscopic sections of the bladder taken at necropsy in 232 cases of urinary tract infection were studied in an attempt to determine a preclinical stage of the condition and explain the lesion of malacoplakia.

Malacoplakia is probably caused by an infectious process in the urinary tract. The presence of large phagocytic cells and Michaelis-Gutmann bodies has not been explained.

I wish to thank Dr. Walter H. Shelden of the Department of Pathology for his advice and aid in the preparation of this paper.

## VAGINAL TRANSILLUMINATION IN SUPRAPUBIC REPAIR OF VESICOVAGINAL FISTULA

E. CLAY SHAW

Surgical authorities appear fairly equally divided in their choice of operative approach for vesicovaginal fistula. This report will deal entirely with the suprapubic transvesical operation, but no criticism will be directed toward the vaginal operation that so many surgeons have performed successfully. Use of an instrument in the vagina, to serve the dual purpose of elevating the operative field and transilluminating the tissues to be dissected, was found to facilitate the ease and effectiveness of the transvesical operation. The principle is simple and obvious, and probably has been used before.

This series of operations was begun nearly twenty-five years ago. The first instrument used was the original cold curved Cameron light with a cork around the tip to prevent the instrument slipping through the fistula into the bladder. More recently, Mr. Frederick J. Wallace of American Cystoscope Makers, Inc. has provided us with a slightly modified instrument (fig. 1) that can be attached to a regular cystoscopic battery box.

For free manipulation of the light it is preferable that the patient be on a table that allows the legs to be separated and the knees to rest on crutches. An assistant stands between the legs and manipulates the light under the direction of the operator. By depressing the handle of the instrument and applying mild pressure, the base of the bladder can usually be elevated one to two inches without distortion. This increased accessibility of the operative field is a great help when the patient is an obese woman.

It is often desirable, during the dissection of the bladder from the vaginal wall, to turn off the overhead lights and to depend entirely on the vaginal light for illumination of the operative field. Transillumination of the flaps will enable the operator to be constantly aware of the thickness of the tissue and reduce the likelihood of buttonholing. Manipulation of the vaginal instrument allows blood from the operative field to drain into the vagina and reduces sponging to a minimum.

Transillumination is especially useful during the closure as it provides accuracy in determining the effectiveness of each of the suture layers.

A series of fourteen consecutive cases of vesicovaginal fistula have been operated successfully by the suprapubic transvesical approach. A vaginal transilluminator was used in all the operations with the exception of the first case. All the fistulas resulted from injuries during pelvic surgery. They varied in size from that of a lead pencil to those in which two fingers could be introduced through the fistula into the bladder. At least 6 cases had been subjected to one or more previous unsuccessful repair operations. There were 2 cases in which four vaginal operations had failed to close the fistula.

Nothing new in operative technique will be offered. However, a few observations will be mentioned that seemed to contribute to the successful result obtained in this series of cases. It appears to be necessary that a sufficient time elapse after

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 5, 1952.

the fistula is produced to allow complete healing of the infected tissue around the fistula before a repair is attempted. There is a tremendous temptation to rush the repair job as all of these women are miserable, and some are on the verge of a psychosis. Nevertheless, a premature attempt to suture friable infected tissue may readily result in failure and it is extremely desirable for all concerned that the first repair attempt be successful. In all cases in this series a minimum period of 4 months was allowed to elapse before the repair operation was performed. As a second requirement, it appears that the bladder should be dissected away from the vagina sufficiently so that closure can be made without tension. Curved scissors with small blades and a long handle is a useful instrument in making the dissection. Care should be used that neither the vaginal nor bladder layer be buttonholed. This procedure must be done well and may take quite a bit

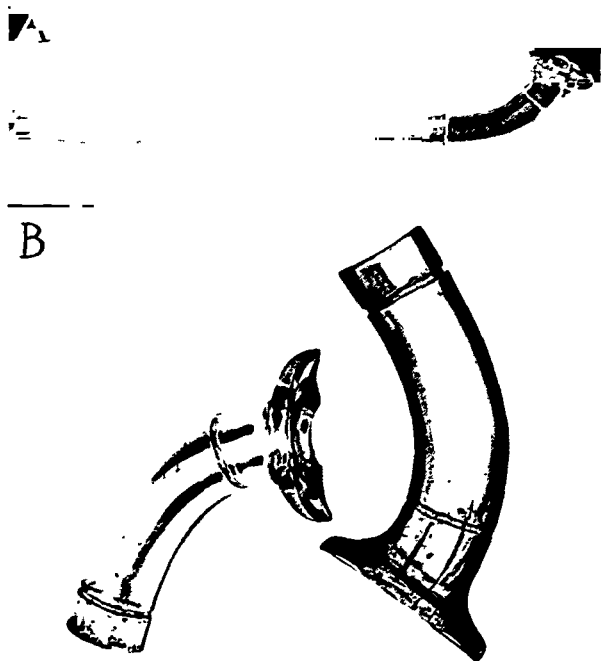


FIG. 1

of time. If the ureteral orifices are sufficiently near that trauma to these structures is feared, ureteral catheters should be inserted, and, if necessary, left in place for several days after the operation. In two instances in this series, the ureteral orifice was on the margin of the fistula. A ureteral meatotomy put the new orifice sufficiently laterally to allow easy closure. There was considerable variation in the cases and it appeared unwise to adopt a routine method of closure. In nearly all instances the closure was made in three layers: first, vaginal wall; second, bladder musculature; and third, submucosa and mucosa. In the larger fistulas, the bladder layers were sutured at right angles to the suture of the vaginal layer. In smaller fistulas, a purse string suture was used for closure of the vaginal layer. The condition of the bladder flaps and the location of the ureteral orifices determined whether the closure of the bladder layers were made horizontally or

transversely. An effort was made to suture in the direction that produced the least tension.

Undoubtedly, the bladder end of a vesicovaginal fistula is the most important so far as closure is concerned. In all the operations, a continuous suture of triple zero chromic catgut on an atraumatic needle was used to close the muscular wall of the bladder, and another suture layer of similar material was used for the closure of the submucosa and mucosa. It is important that the tissues at the site of closure should be heaped up to a thickness even greater, if possible, than the normal walls between the vagina and the bladder. Here again, transillumination from the vaginal light is helpful.

The suprapubic drainage attending the transvesical operation appears to be a real advantage. A large mushroom catheter inserted into the bladder and tied snugly to the upper anterior wall will give adequate drainage without contacting the trigone. A retention urethral catheter must, of necessity, remain in contact with the suture line. Considerable stress was put on the importance of the drainage tube always remaining unclamped. It has been the custom in recent years, not only to enter this on the chart, but also to post a sign on the head of the patient's bed, that under no conditions should the tube be clamped. As soon as the patient is well out of anesthesia, she is also told of the importance of keeping the drainage tube open. This is to avoid the occasional thoughtlessness of student nurses who might forget to remove a clamp from the tube after a patient's bath, or after her bed is made. As a rule, bladder irrigations were not done.

At least one-half of these patients were operated on before sulfa drugs and antibiotics. In these earlier cases, the meager urinary antiseptics that were at our disposal were used vigorously. Since the advent of sulfa therapy, penicillin and the newer antibiotics, the task of keeping the urine relatively sterile has been greatly eased.

There appears to be no necessity of putting the patient in a specific uncomfortable position or in any way restricting her movement in bed. Should any tendency develop toward tenesmus or bladder irritation, which rarely happens, she should be given as much opiates as are necessary to give her complete relief.

With two exceptions, the drainage tube was allowed to remain for 20 days in all cases in this series. It is probably unnecessary to leave the tube in for such a long time. However, the success attending the earlier operations in the series made us reluctant to experiment with shorter drainage periods. It would seem that ample time should be allowed for absorption of the catgut sutures and for the production of adequate scar tissue before subjecting the operative area to tension.

#### SUMMARY

A series of 14 consecutive successful cases of suprapubic repair of vesicovaginal fistula has been presented. A combined vaginal tractor and transilluminator has been described. The tractor feature of this instrument serves to elevate the bladder floor and render the operative field more accessible. The transillumination feature aids in the dissection of the layers and in determining the effectiveness of the repair.

*1714 Biscayne Blvd., Miami 32, Fla.*



## VESICAL NECK OBSTRUCTIONS IN CHILDREN

HAROLD P. McDONALD, WILBORN E. UPCHURCH AND CLINTON E. STURDEVANT

In speaking of vesical neck obstructions in children, one usually refers to congenital lesions. The symptoms vary a great deal depending on the severity of the obstruction and whether or not infection is present. There is also a great variation in the resultant damage done to the bladder and upper urinary tract. Due to the wide variation in symptoms, and also because of the failure of many doctors to suspect vesical neck obstruction as a likely cause for unexplained fever, recurrent or persistent pyuria, urgency, frequency, or restricted urinary stream, a large percentage of these little patients suffer irreparable renal damage before relief of the obstruction is undertaken.

The purpose of this paper is to call attention to the prevalence of these bladder neck lesions in children, emphasizing the importance of early recognition and correction so that damage to the upper urinary tract may be prevented or lessened. It shall be pointed out that a great many children with recurrent pyuria, pyelitis, urgency, frequency, and other urinary symptoms are suffering from vesical neck obstruction.

Enuresis as a symptom of bladder neck obstruction is especially emphasized because of the general lack of understanding of this problem by family doctors, pediatricians and even many urologists. As regards enuresis, parents too often are told to wait and probably the child will "outgrow it"; while the little patient is "out-growing" his trouble, his psychological development may be warped while the continued back pressure of the obstruction may cause kidney damage that makes him a renal cripple in later years.

Urologists should call attention to these facts at every opportunity, especially before local county and state societies. The practice of giving urinary antiseptics to children with pyuria without proper urological investigation should be condemned vigorously and continually. It should be regarded as equally improper to "treat" pus in the urine as it is to "treat" blood in the urine. In children, this should be even more condemned; because of the delicate nature of the urinary apparatus, delay in diagnosis has so often resulted in damage to bladder and kidneys beyond repair.

It is our opinion that bladder neck obstructions are a great deal more common than generally has been believed. This is borne out by the fact that an increasing number of these children are being seen by us and by others. Reports by Howard and Buchtel and by Burns and Harvard (1951) indicate the increasing awareness of the frequent occurrence and importance of vesical neck obstructions in children. Also a report by Peyton in the *Journal of Urology* (January 1953) of a study of bladder neck obstructions in young adult males, indicates that many of the bladder symptoms of young men in the Army are due to this cause. It appears likely that such obstructions are congenital in origin and might have been corrected in early life had they been suspected and looked for.

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 3, 1952.

Congenital obstructions at the vesical neck may be classified as contractures or valve formations, the former observed more often in girls and the latter more often in boys. Another type of obstruction seen in boys is due to hypertrophy of the verumontanum.

All patients with vesical neck obstructions may be divided into three main groups depending upon the severity of the obstruction, whether mild, moderate or severe.

It is important that each child be evaluated as to the grade of obstruction in terms of upper urinary tract damage. Patients with mild obstructions may have little or no residual urine, and there may be little or no dilatation of the ureters or renal pelves. Kidney function may be essentially normal. Pyelograms may show nothing abnormal. Cysto-urethroscopy with a foroblique telescopic instrument such as the McCarthy miniature cystoscope reveals a small to moderate degree of trabeculation and hyperemic vesical neck masses or other obstructive lesion. Trabeculation in the bladder wall is considered positive proof of vesical neck obstruction. Residual urine need not be present in appreciable amount as it is found only after the bladder begins to decompensate, due to back pressure of voiding against obstruction. Children showing marked bladder trabeculations with residual urine and dilatation of the upper tracts are classified as having severe obstruction. The management of a patient with such marked or neglected vesical neck obstruction is usually a long term proposition. The child should be observed over a period of many years and multiple operations may be necessary in order for the best end results in terms of adult renal function.

In a study of 112 children with bladder symptoms seen by us during the past 10 years, the age variation was from 8 hours to 14 years. There were 45 girls and 67 boys. The symptoms or complaints were: enuresis, 65; frequency, 38; urgency, 36; dysuria, 41; pyuria, 32; straining to void, 21; fever, 16; fever of unexplained origin, 6; pain or soreness over bladder, 12; acute retention, 3; overflow incontinence, 1.

Examination revealed that 57 of these children had a narrow urethral meatus; 42 had stricture in the urethra; 27 had vesical neck masses or hypertrophy; 17 had vesical neck contracture or bar; 14 had valve-like formations in the deep urethra; and 2 had hypertrophy of the verumontanum. The presence of multiple obstructions was noted in many of these patients; hence of those observed with a narrow urethral meatus and or stricture of the urethra, 57 and 51 respectively, many also had vesical neck obstruction as well.

In former years this fact was not well recognized and it is very likely that a great many of these children seen in prior years had unrecognized vesical neck obstruction as well as narrow meatus and urethral stricture. A greater awareness of this possibility of multiple congenital obstructions has shown such to be the case in numerous instances.

This occurrence of multiple congenital obstructions has been noted and recently reported by Campbell, Howard and Buchtel, Burns and Harvard and others.

One girl baby with pyuria, seen at the age of 18 months, had suffered numerous

bouts of fever all her life and was found to have a narrow urethral meatus, vesical neck masses with contracture of the bladder outlet, bilateral stenosis of the ureterovesical openings and bilateral ureteropelvic obstruction. This little patient has made a remarkable recovery over a period of 3 years following multiple operations, including urethral meatotomy, numerous urethral dilations, three vesical neck resections and fulgurations and bilateral ureteropelvic plastic operations with nephrostomy and intubation of the ureters.

Treatment of children with vesical neck obstructions of mild degree usually consists of fulguration of the vesical neck masses through a miniature cystoscope or a panendoscope using a conical or ball type electrode. The size instrument used depends upon how easily the urethra may be dilated. In most girls a size 24F may be used while most boys must be treated with smaller instruments unless perineal urethrotomy is done. The fulguration is done in two or more stages, at about eight week intervals, one side or one half of the circumference of the vesical neck being destroyed at a time. Meatotomy and urethral dilations are done as indicated and also bladder dilations under anesthesia when capacity is found to be subnormal.

In small boys or in those with congenitally narrow urethras that do not dilate readily, a button hole perineal urethrotomy, as recommended by Nesbit, may be done for insertion of the instrument into the bladder.

Classified as moderate obstructions are those of larger hypertrophic masses or definite contractures at the vesical neck. There may be a small amount of residual bladder urine. Trabeculations are more pronounced than are observed in patients classified as having mild obstructions. A moderate amount of back pressure dilatation and some damage to renal parenchyma may be found. In treatment of this group of patients, transurethral resection with an infant resectoscope is preferred to fulguration, which, because of the larger mass of obstructing tissue present, may be followed by sloughing, and secondary hemorrhage, or prolonged healing time. Care must be exercised in the use of the infant resectoscope due to the possibility of sphincter damage.

Treatment of patients with severe obstructions is usually a long term proposition. Classified in this group are children with obstructions of such degree or of such long standing as to produce a great back pressure damage, evidenced by marked trabeculations or cellules in the bladder wall, large dilated ureters and pelves and considerable damage to the renal parenchyma, much of which is permanent. Suprapubic puncture or cystostomy for bladder drainage has been found important in most patients in this group.

Failure to recognize this need for suprapubic drainage to bypass the obstruction resulted in death of one of our patients from severe pyelonephritis. The tube should be kept in for such time as is deemed necessary to allow stabilization and maximum recovery from renal damage. In 3 patients in our series, all boys with severe obstruction and a great deal of kidney damage, a suprapubic drainage tube was used for 5, 6, and 8 years respectively. It is conceivable that sufficient bladder and upper urinary tract damage might occur as to make permanent suprapubic drainage necessary.



FIG. 1. *A*, endoscopic photograph of vesical neck obstruction in 9 year old boy. *B*, photograph of vesical trabeculations in same boy. *C*, photograph of resected pieces removed through McCarthy infant resectoscope.

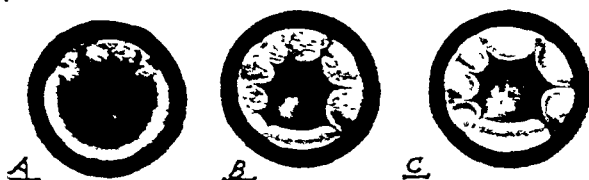


FIG. 2. Types of vesical neck obstructions encountered in children. *A*, papillomatous appearance seen often in enuretic girls. *B*, inflammatory masses also seen in enuretics. *C*, masses with more obstruction seen in both girls and boys



FIG. 3. Hydronephrosis in children with vesical neck obstruction. *A*, minimal hydronephrosis and hydro-ureter. *B*, moderate hydronephrosis and hydro-ureter. *C*, marked dilatation of upper urinary passages with irreparable damage to kidneys.

After stabilization by drainage and control of infection, proper measures for the complete removal of the obstruction at the bladder neck are undertaken. Other corrective procedures are also done according to indication.

Transurethral resection of the obstructing bar or bladder neck contracture is preferred by us and also by Campbell and by Howard and by Buchtel. Burns

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Treatment of children with vesical neck obstructions of mild degree usually consists of fulguration of the vesical neck masses through a miniature cystoscope or a panendoscope using a conical or ball type electrode. The size instrument used depends upon how easily the urethra may be dilated. In most girls a size 24F may be used while most boys must be treated with smaller instruments unless perineal urethrotomy is done. The fulguration is done in two or more stages, at about eight week intervals, one side or one half of the circumference of the vesical neck being destroyed at a time. Meatotomy and urethral dilations are done as indicated and also bladder dilations under anesthesia when capacity is found to be subnormal.

In small boys or in those with congenitally narrow urethras that do not dilate readily, a button hole perineal urethrotomy, as recommended by Nesbit, may be done for insertion of the instrument into the bladder.

Classified as moderate obstructions are those of larger hypertrophic masses or definite contractures at the vesical neck. There may be a small amount of residual bladder urine. Trabeculations are more pronounced than are observed in patients classified as having mild obstructions. A moderate amount of back pressure dilatation and some damage to renal parenchyma may be found. In treatment of this group of patients, transurethral resection with an infant resectoscope is preferred to fulguration, which, because of the larger mass of obstructing tissue present, may be followed by sloughing, and secondary hemorrhage, or prolonged healing time. Care must be exercised in the use of the infant resectoscope due to the possibility of sphincter damage.

Treatment of patients with severe obstructions is usually a long term proposition. Classified in this group are children with obstructions of such degree or of such long standing as to produce a great back pressure damage, evidenced by marked trabeculations or cellules in the bladder wall, large dilated ureters and pelves and considerable damage to the renal parenchyma, much of which is permanent. Suprapubic puncture or cystostomy for bladder drainage has been found important in most patients in this group.

Failure to recognize this need for suprapubic drainage to bypass the obstruction resulted in death of one of our patients from severe pyelonephritis. The tube should be kept in for such time as is deemed necessary to allow stabilization and maximum recovery from renal damage. In 3 patients in our series, all boys with severe obstruction and a great deal of kidney damage, a suprapubic drainage tube was used for 5, 6, and 8 years respectively. It is conceivable that sufficient bladder and upper urinary tract damage might occur as to make permanent suprapubic drainage necessary.



FIG. 1. *A*, endoscopic photograph of vesical neck obstruction in 9 year old boy. *B*, photograph of vesical trabeculations in same boy. *C*, photograph of resected pieces removed through McCarthy infant resectoscope.



FIG. 2. Types of vesical neck obstructions encountered in children. *A*, papillomatous appearance seen often in enuretic girls. *B*, inflammatory masses also seen in enuretics. *C*, masses with more obstruction seen in both girls and boys.

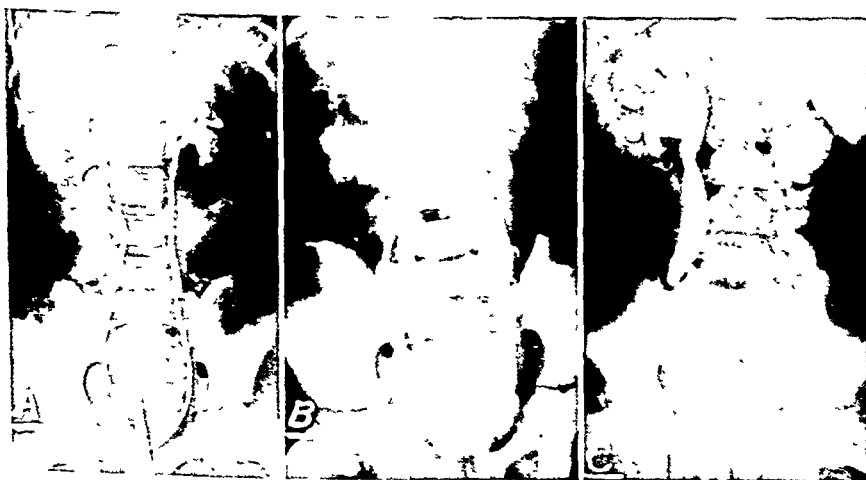


FIG. 3. Hydronephrosis in children with vesical neck obstruction. *A*, minimal hydronephrosis and hydro-ureter. *B*, moderate hydronephrosis and hydro-ureter. *C*, marked dilation of upper urinary passages with irreparable damage to kidneys.

After stabilization by drainage and control of infection, proper measures for the complete removal of the obstruction at the bladder neck are undertaken. Other corrective procedures are also done according to indication.

Transurethral resection of the obstructing bar or bladder neck contracture is preferred by us and also by Campbell and by Howard and by Buchtel. Burns

and Harvard have recommended a modified retropubic approach. The relative merits of these two approaches to the problem will not be discussed here. Whether by transurethral resection or by open operation, the important thing is complete removal of the vesical neck obstruction and correction of whatever other abnormalities may be found.

A patient illustrating severe obstruction with a great deal of renal damage was seen at the age of 22 months. The bladder was greatly distended and there was overflow incontinence. Suprapubic cystostomy was done and 30 ounces of uninfected urine was obtained. The suprapubic tube was worn for a period of 6



FIG. 4. A, cystogram showing vesical neck obstructing masses with reflux up dilated ureters and renal pelvises. B, same patient 4 years after two vesical neck resections and suprapubic drainage.

years during which time urethral meatotomy, urethral dilatations and two transurethral resections of the bar and contracted vesical neck were done. Growth and development were normal, renal function improved phenomenally, and the dilated ureters and pelvis contracted considerably. Some dilatation and impairment of the upper urinary tract remain and, quite likely, may be permanent. However, the boy now 11 years old, voids a fine stream, completely empties his bladder, has clear, uninfected urine and vows he is going to study medicine and some day help us practice urology. (See figures 1, 2, 3, 4.)

#### SUMMARY

Congenital obstructions at the vesical neck are much more common than generally has been believed. A great many children who have enuresis, frequency, urgency, nocturia, pyuria, or recurrent fever of unexplained origin, or other symptoms referable to the urinary tract have, as the basic cause, obstruction at the vesical neck. Careful history and examination will often reveal the presence of such a lesion hitherto unsuspected.

Recognition of and correction of less severe and milder obstructing lesions are important in stopping enuresis and in preventing psychological mal-adjustments often seen in children who have enuresis, urgency, and frequency. The less severe obstructions also may be the beginning of obstructive lesions at the bladder neck seen in young adult males which have recently been recognized and reported. Many multiple obstructions and some bladder neck obstructions of mild or less severe degree may be overlooked unless suspected and a careful evaluation made. Early recognition and correction of severe obstructive lesions are of prime importance in order that progressive renal damage may be prevented or stopped. In children with such severe obstructions and considerable back pressure renal damage, suprapubic drainage is an important stabilizing measure preparatory to corrective surgery.

*57 Forsyth St., N.W., Atlanta, Ga.*

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## BILATERAL ADRENALECTOMY FOR PROSTATIC CANCER

PETER L SCARDINO, CHARLES L PRINCE AND THOMAS A MCGOLDRICK

The purpose of this work is to present clinical and laboratory evidence to support the thesis that bilateral total adrenalectomy is an acceptable procedure for the treatment of selected cases of metastatic prostatic carcinoma which have failed to respond to or have escaped from other methods of anti-androgenic control

The concept of anti-androgenic control of metastatic prostatic cancer is based primarily on the fundamental work of Huggins who in 1941 demonstrated the inhibiting effect of estrogens and the stimulating effects of androgens on prostatic physiology<sup>1 2</sup> This work was facilitated by studies of the enzyme acid phosphatase and its relation to normal and neoplastic processes in the prostate gland<sup>3</sup> Originally it had been noted that malignant prostatic tissue was frequently an "overgrowth of adult epithelial cells which like other adult prostatic epithelium underwent atrophy when androgenic hormones were reduced in amounts or inactivated"<sup>2</sup> Gomori stained prostatic tissue slices and blood serum determinations revealed greatly decreased amounts of the enzyme acid phosphatase following the administration of estrogens and orchiectomy<sup>4</sup>

Sufficient time has elapsed since the announcement of this fundamental work to draw certain conclusions relative to the hormonal treatment of prostatic cancer While a prompt response to anti-androgenic therapy has been noted in many patients with metastatic prostatic cancer, frequent failures have necessitated continued investigation Many possibilities have been suggested to explain these failures: differences in histologic or biologic characteristics of prostatic carcinoma,<sup>5</sup> inherent cell differences, the establishment of autonomy by the prostatic neoplasm and its independence of androgenic influence,<sup>6 7 8</sup> the influence of extragonadal sources of androgen upon prostatic tissue,<sup>6 9 10</sup> and possible basic metabolic differences in the host<sup>11</sup>

A clearer understanding of the failures has been gained from an investigation of adrenal physiology Gonadectomy in susceptible strains of mice results in the development of benign or malignant tumors of the adrenal cortex preceded by cortical hyperplasia<sup>12</sup> The intact hypophysis stimulates adrenal hyperactivity

This work was made possible through the support of the Louisa Porter Aid Society and the cooperation of the Central Of Georgia Railroad Hospital

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in the absence of gonadal hormones.<sup>12</sup> Such laboratory evidence has been substantiated by clinical observations. In patients no longer responding to anti-androgenic treatment enlargement of the adrenals to several times their normal size has been observed.<sup>5</sup> The role of the pituitary gland in stimulating the adrenals to produce androgens after castration has been studied in conjunction with urinary excretion of gonadotrophic hormones and 17-ketosteroids.<sup>13</sup> Following orchiectomy, urinary excretion of gonadotrophins and 17-ketosteroids is usually increased, due to the lack of inhibitory actions of specific testicular hormones.<sup>5</sup> However, this increased excretion may be counteracted for varying periods of time by the immediate administration of estrogens after orchiectomy.

The results of orchiectomy and estrogen administration were so encouraging that further efforts to remove other sources of androgens were inevitable. Two routes of attack were open. A somewhat more difficult and poorly understood route was that of hypophysectomy.<sup>14</sup> A more direct and less hazardous route was adrenalectomy. Having observed an increase in extragonadal androgen production following the use of estrogens and orchiectomy, it was obvious that an effort should be made to remove this extragonadal source. In spite of an incomplete and inadequate supply of adrenal substitution materials, Huggins and his group in 1945 performed the first total adrenalectomies on four patients with uncontrollable metastatic prostatic cancer.<sup>6</sup> However, only one survived long enough to be studied under adrenal substitution therapy. In this patient androgenic activity was apparently abolished as evidenced by 17-ketosteroid determinations but the carcinoma progressed. This patient succumbed 4 months after operation to adrenal insufficiency. In spite of laboratory evidence to the contrary, the patient showed subjective improvement.

Before pursuing this study investigators awaited the promised supply of adrenal cortical steroids and knowledge gained therefrom.<sup>15</sup> The successful use of adrenal substitution materials following total adrenalectomy for hypertension justified the application of this procedure for metastatic uncontrollable prostatic cancer. Others investigating prostatic cancer undertook a similar study which has added much to our knowledge of adrenal physiology and prostatic cancer.<sup>16, 17</sup>

On July 11, 1951, the first patient in our series underwent adrenalectomy for advanced prostatic cancer.

#### METHODS AND MATERIALS

The study was made on three patients with demonstrable bone metastases and local extension of prostatic cancer outside the prostatic capsule who had previously undergone orchiectomy, received estrogenic therapy and in one instance cortisone therapy (case 1). (Case 2 previously had undergone radical perineal prostatectomy). All relapsed and after varying periods of time were treated by bilateral adrenalectomy.

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1. The surgical technique employed was a modified Young posterior approach in which the patient is placed in the prone position permitting simultaneous bilateral incisions approximately 5 cm. from the midline at the level of the eleventh costovertebral angle extending laterally parallel to the twelfth rib. In

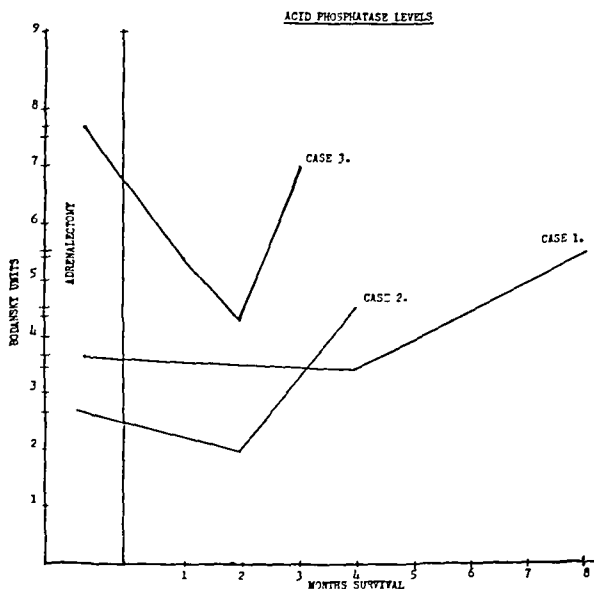


FIG. 1. Phosphatase chart. Initial decrease in serum acid phosphatase is seen in each case with subsequent rise.



FIG. 2. Case 1. X-ray of pelvis shows saturation with metastases. Roentgenograms in cases 2 and 3 were similar.

cases 1 and 3 the twelfth ribs were removed. The remainder of the procedure conforms to Young's description.<sup>18</sup>

2. Serum phosphatase determinations made before adrenalectomy on all three

<sup>18</sup> Young, Hugh H.: Surg., Gynec. & Obst., 63: 178, 1936.

patients revealed an elevation of the acid phosphatase in the three cases. Following adrenalectomy there occurred a measurable decrease in serum acid phos-

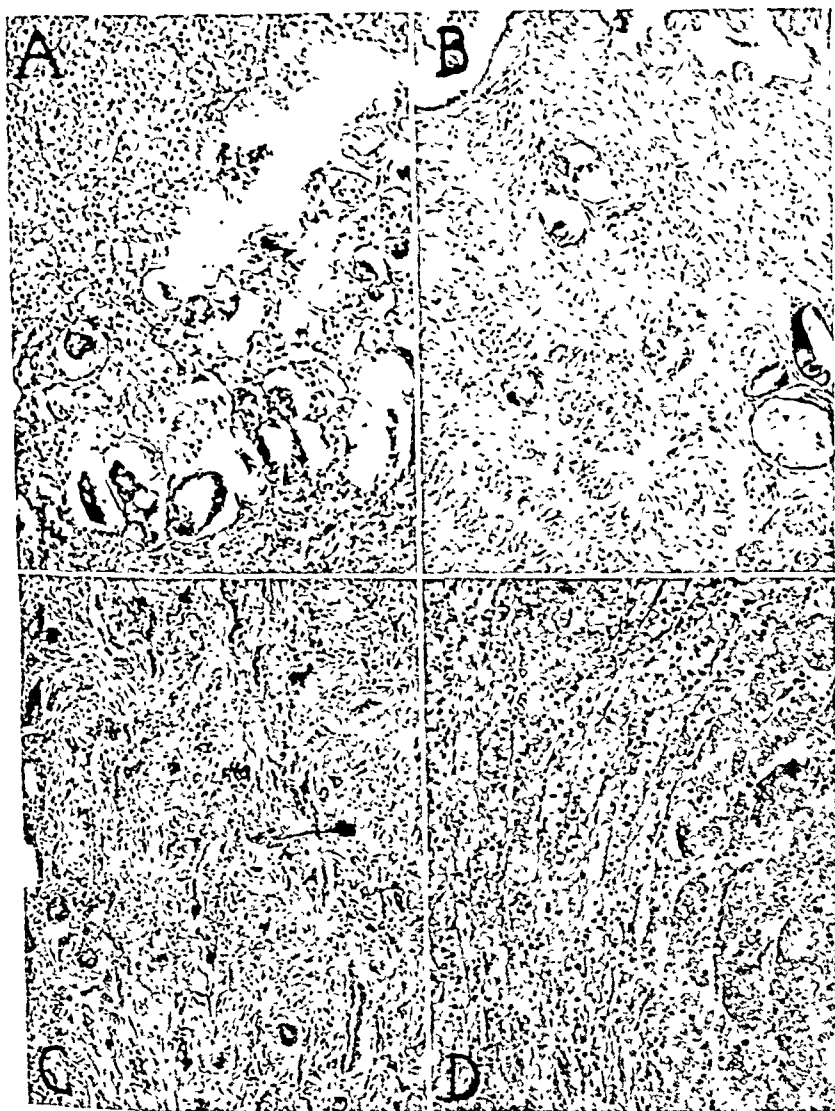


FIG. 3. *A* and *B*, case 1. *A*, adrenal gland. Normal adrenal tissue with scattered areas of metastatic prostatic carcinoma. *B*, prostate gland 6 months after treatment. Visible acini are few in number. Gland is replaced by fibromuscular tissue. *C* and *D*, case 2. *C*, prostate after estrogens; before adrenalectomy. Undifferentiated prostatic carcinoma could not be made from these sections nor by special stains. *D*, adrenal gland. Metastatic undifferentiated prostatic carcinoma.

phatase. A gradual elevation to and above the preoperative level occurred in 3 patients (fig. 1).

3. Of the 3 cases, two had roentgenologically demonstrable saturation metastases in the pelvis, spine and femurs (fig. 2). The predominant lesion was

osteoplastic. In case 2 only pathologic compression fracture of the first lumbar vertebra was demonstrated. None of the patients had symptoms of urinary obstruction.

4. The erythrocyte count in case 1 was 1.86 million prior to orchiectomy and estrogen therapy. This patient demonstrated the clotting defect seen in carcinoma of the prostate.<sup>19, 20</sup> (See below for further details in case history.) Following orchiectomy but prior to adrenalectomy the erythrocyte count in case 1 was 3.8 million. Case 2 maintained an erythrocyte count above 4.0 million at all times. Except following multiple blood transfusions, the erythrocyte count in case 3 remained at approximately 2.5 million at all times.

TABLE 1. *Original schedule.* (Used in case 1.) Adapted from Thorn et al. (Now considered over treatment.)

|                               |                                                                                                                                                                                                                             |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Op - 3 and op - 2 day.</i> | ACTH 10 - 25 mg. q. 6 h.                                                                                                                                                                                                    |
| <i>Op - 1 day.</i>            | ACTH q. 6 h.<br>Cortone 100 mg. 12 hrs. pre-op.<br>Cortone 50 mg. 2 hrs. pre-op.                                                                                                                                            |
| <i>Op - day.</i>              | 200 cc continuous aqueous adrenal cortical extract during operation.<br>Neosynephrin 10 mg. in 1000 cc saline titrated for hypotension.<br>Whole blood for refractory hypotension.<br>Start 50 mg. cortone q. 8 h. post op. |
| <i>Op + 1 day.</i>            | Cortone 50 mg. q. 8. h.<br>Sod. chloride 8 gm. daily (2-3 days).                                                                                                                                                            |
| <i>Op + 2 day.</i>            | DOCA 1-2 mg. daily as needed for blood pressure.                                                                                                                                                                            |
| <i>op + 3 day.</i>            | Gradual reduction of cortone dosage, ultimately to 25 mg. or 12.5 mg. daily.                                                                                                                                                |

5. Histologic studies of the adrenal glands: case 1 showed a well differentiated metastatic adenocarcinoma in both adrenal glands; case 2 showed undifferentiated metastatic carcinoma of both adrenal glands and an adjacent lymph node; in case 3 the adrenal glands revealed no carcinoma; the prostatic sections in cases 2 and 3 revealed undifferentiated carcinoma with wide spread direct extension into the periprosthetic tissues (fig. 3).

#### PRE- AND POSTOPERATIVE MEDICAL MANAGEMENT

Complete removal of both adrenal glands presents the problem of management of acute adrenal insufficiency on the day of operation. This is accomplished as described in tables 1, 2 and 3 and is based on the principle of maintaining a maximal concentration of circulating steroids. The long range control of chronic adrenal insufficiency (Addison's disease) is described in table 4. It is apparent that the management of these patients has been greatly simplified by the avail-

<sup>19</sup> Seale, R. A., Jampolis, R. W. and Barga, J. A.: Surg. Clin. North Amer., **31**: 1111, 1951.

<sup>20</sup> Tagnon, H. J., Whitmore, W. F., Jr. and Shulman, N. R.: Cancer, **5**: 9, 1952.

ability of current parenteral and oral steroid preparations. We have been impressed by the fact that the acute and chronic phases were managed safely and relatively easily with less replacement therapy than was originally believed pos-

TABLE 2. *Revised schedule* (Used in cases 2 and 3.) Adapted from Huggins and Bergenstal

|                    |                                                                                                                                                                             |
|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Op - 1 day.</i> | Cortone 50 mg. q. 6 h.<br>DOCA 5 mg. (one dose).<br>Sodium chloride 5 gm.                                                                                                   |
| <i>Op - day.</i>   | Cortone 150 mg pre-op and 50 mg. q. 6 h. post op.<br>DOCA 5 mg. (one dose).<br>Fluids and blood; nor-epinephrine for acute hypotension.<br>Aqueous extract <i>not</i> used. |
| <i>Op + 1 day.</i> | Cortone 50 mg. q. 6 h.<br>DOCA 5 mg. (one dose).<br>Sod. chloride 3 gm. (by mouth)                                                                                          |
| <i>Op + 2 day.</i> | Cortone 50 mg. q. 12 h.<br>DOCA 3 mg. p.r.n.<br>Sod. chloride 3 gm.                                                                                                         |

Gradual reduction steroids to maintenance dose; DOCA *not* required for maintenance.

TABLE 3. *New schedule* (Note reduction in medication.)

|                    |                                                                                                                                                                |
|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Op - 1 day.</i> | Cortone 100 mg. 12 hrs. pre-op.<br>ACTH and DOCA <i>not</i> used.                                                                                              |
| <i>Op - day.</i>   | Cortone 100 mg. pre-op.<br>Aqueous extract <i>not</i> used.<br>Neosynephrin or nor-epinephrine for hypotension.<br>Blood and fluids.<br>Cortone 50 mg. q. 6 h. |
| <i>Op + 1 day.</i> | Cortone 50 mg. q. 6 h.<br>Sod. chloride p.r.n.<br>DOCA <i>not</i> always necessary post op.                                                                    |

(Note expense much less) Protection adequate.

TABLE 4. *Maintenance therapy*

1. Cortone 25 mg. or 12.5 mg. daily.
2. Generous salt added to food. (Tablets *not* required.)
3. Emphasize patient's dependence on daily ration of cortone.
4. Treat intercurrent stress, infection, operation etc., as would Addison's disease: Immediate increase in cortone and salt. Intensive antibiotics.
5. DOCA *not* required for maintenance in our experience.
6. Routine estrogenic therapy continued.

sible. General anesthesia (cyclopropane) has proven satisfactory in all cases, although in adrenalectomy performed for hypertension, continuous spinal anesthesia is preferable. We have had no experience with this group. A constant worry at the time of operation is the sudden profound hypotension which may follow the removal of both glands. We have not encountered this complication, ap-



parently because of adequate preoperative protection. When this occurs, intravenous neosynephrin or nor-epinephrine usually will restore promptly the blood pressure to normal levels. Whole blood is effective in controlling a refractory postoperative hypotension.

#### GENERAL CLINICAL COURSE AFTER ADRENALECTOMY

Following the immediate postoperative period the patients showed a varying response to the procedure.

1. *Subjective and neurological changes.* Within 10 to 12 days following adrenalectomy, all three patients noted partial to complete cessation of pain. This was outstanding in case 1. This patient had required large doses of narcotics for 2 months prior to surgery but following the immediate postoperative period and subsequently has required absolutely no sedation or narcotics. His appetite has improved. He has gained 45 pounds in weight. In case 2 the predominant symptom was pain related to the pathologic fracture of the first lumbar vertebra. He also experienced severe rectal tenesmus and frequent bowel movements but following adrenalectomy there was a decrease in the frequency of stools and rectal tenesmus and he required smaller doses of opiates to control the back pain. For two weeks his appetite improved with a resultant five pound gain in weight. However, the metastatic carcinoma in the spinal cord resulted in paraplegia and death. (Complete details follow in case history.)

2. *Clinical changes in the primary lesions following adrenalectomy.* In case 1 there had been partial regression of the local lesion following orchiectomy and complete regression following adrenalectomy. The diagnosis of prostatic carcinoma can no longer be made by rectal palpation. In case 2 there was incomplete regression of the prostatic lesion following adrenalectomy but sufficient change to permit a well formed stool without rectal tenesmus. In case 3 the survival time was insufficient for satisfactory evaluation of changes in the local lesion.

3. *Changes in roentgenograms of bony metastases after adrenalectomy.* There have been no demonstrable changes.

#### REPORT OF CASES

*Case 1.*—O. W., a white man 52 years of age, was admitted to the hospital on November 2, 1949 complaining of pain in the lower extremities and back, exertional dyspnea, anorexia and loss of weight. There were no urinary symptoms. Following extraction of two teeth, uncontrollable hemorrhage occurred which required multiple blood transfusions and specific vitamins. Hematological studies revealed a marked suppression of the hemopoietic system as reflected in red blood cells, 1.86 million; hemoglobin, 40 per cent, bleeding time, 4 minutes, 30 seconds; clotting time, 5 minutes, 20 seconds; prothrombin time, 22 with control 20; platelet count 19,000. Examination revealed an extensive carcinoma of the prostate which on rectal examination was fixed, stony hard, nodular and irregular, with extension into the seminal vesicles and base of the bladder and with protrusion into the rectal lumen without perforation of the rectal mucosa. The anus only partially admitted the examining index finger. The acid phosphatase was

3.3 Bodansky units. A complete radiological survey revealed no bony abnormalities of the skull but there were metastases compatible with metastatic prostatic carcinoma to the lumbar vertebra, pelvis, shoulders and femur. Following multiple blood transfusions, estrogenic therapy and bilateral orchiectomy on December 12, 1949, the patient gained weight and became free of pain, but required intermittent multiple blood transfusions. After one year, the bone pain recurred and he again required large doses of narcotics. In spite of increasing the estrogen dosage and the institution of cortisone therapy (100 mg. daily) the patient continued to lose weight and increasingly large doses of opiates were necessary. After adequate medical preparation, bilateral adrenalectomy was performed on July 11, 1951. The immediate postoperative course was stormy, but with adequate adrenal substitution therapy the patient recovered, and was without pain on the fourteenth postoperative day and has since remained symptom free. He has gained 45 pounds in weight and has returned to work. The latest acid phosphatase determination was 4.2 Bodansky units. There have been no changes in the x-ray studies. A normal blood picture has been re-established.

*Case 2.* G. B., a 57 year old white man, was admitted to the hospital on September 5, 1951 complaining of anorexia, weight loss, general malaise, back pain, increasing constipation with frequent small caliber stools and marked rectal tenesmus. There were no urinary symptoms. In January 1949, following preoperative estrogen therapy in an attempt to reduce the size of the local prostatic lesion, the patient underwent radical perineal prostatectomy elsewhere.<sup>21, 22</sup> He was maintained on small amounts of estrogens. Histological examination of the excised prostate revealed an undifferentiated carcinoma with local extension. The patient escaped from the effects of estrogen therapy and underwent bilateral orchiectomy on April 12, 1950 to which he responded satisfactorily for approximately 12 months. A relapse occurred following which the patient received TACE<sup>23</sup> which produced a very brief remission. His rectal symptoms however again became intolerable as did the back pain which resulted from a pathologic compression fracture of the first lumbar vertebra. Rectal examination of the prostate was difficult due to the encroachment of the local lesion upon the rectal ampulla. The rectal mass was huge, stony hard, irregular, nodular and fixed. The acid phosphatase was 2.5 Bodansky units. Roentgenologically there was a compression fracture of the first lumbar vertebra without other demonstrable metastases. Having escaped all available forms of anti-androgenic therapy, the patient underwent bilateral total adrenalectomy on September 10, 1951. The immediate postoperative course was entirely uneventful. There was considerable prompt relief of back pain and a gradual cessation of rectal symptoms. Also, the local lesion regressed slowly in size and softened. The improvement was never particularly striking although following operation the patient required smaller doses of opiates. The acid phosphatase decreased temporarily to 2.0 Bodansky units only to rise in two months to 3.8 Bodansky units. He was discharged from the hospital

<sup>21</sup> Colston, J. A. C. and Brendler, H.: J.A.M.A. 134: 848, 1947.

<sup>22</sup> Parlow, A. L. and Scott, W. W.: New York State. J. Med., 49: 629, 1949.

<sup>23</sup> Smith, P. G., Rush, T. W. and Evans, A.: J. Urol., 65: 886, 1951.

on September 25, 1951. Follow up examinations revealed continued regression of the rectal lesion, but there was moderate bone pain which was not as severe as before the adrenalectomy. The patient expired in cardiac failure elsewhere in January 1952, four months following the adrenalectomy.

*Case 3.* J. S., a 50 year old Negro, was admitted to the hospital on October 3, 1951 complaining of excruciating pain in the sacro-iliac region, and lower extremities; weight loss of 20 pounds, general malaise and anorexia. The diagnosis of prostatic carcinoma had been made originally in June 1950. At that time the patient was placed on estrogenic therapy. He later escaped from the effects of estrogens and underwent orchiectomy in January 1951. A brief remission of symptoms of approximately 3 months was experienced following orchiectomy and estrogen therapy but again he escaped anti-androgenic therapy and experienced a recurrence of bone pain requiring large doses of narcotics. Examination revealed an emaciated Negro in acute pain. The prostate was nodular, fixed, stony hard, and there was involvement of the periprostatic tissues. Acid phosphatase determination was 7.4 Bodansky units. Radiological survey revealed saturation bone metastases involving all the vertebra and pelvic bones. In view of the persistent downhill course and the failure to respond to conventional anti-androgenic therapy, the patient underwent bilateral adrenalectomy on October 5, 1951. His postoperative course was uneventful. He had an immediate response relative to pain which was objectively reflected in an acid phosphatase determination 20 days postoperatively of 4.4 Bodansky units. His appetite rapidly increased for a brief period, but concurrently he developed a paraplegia with urinary and fecal complications. An exploration of the ninth, tenth and eleventh dorsal vertebra on November 21, 1951 revealed encroachment of metastatic carcinoma upon the spinal cord. The patient again began to require massive doses of opiates. The acid phosphatase rose to 7.0 Bodansky units just prior to death in January 1952. Necropsy: There was extensive carcinomatosis involving the prostatic area, with extension of undifferentiated prostatic carcinoma around the seminal vesicles, into the base of the bladder and involvement of all vertebra and the entire pelvis.

#### COMMENT

Following orchiectomy, adrenalectomy is an effective and acceptable means of removing extragonadal sources of androgens. The objective means at our disposal in helping to evaluate the results of adrenalectomy were serum acid phosphatase determination and examination of the prostatic lesion. Although evaluation of subjective changes is at best only partially reliable, a persistent subjective change of 9 months' duration is perhaps an acceptable criterion. In case 1 a 9-month follow up has shown a subjective return to normal and an objective response as evidenced by the decreased serum acid phosphatase and regression of the local lesion. A slight elevation of recent acid phosphatase determinations might presage incipient relapse.

Thus far it has been impossible to satisfactorily explain the variations in response to anti-androgenic therapy. It is probable that unsatisfactory results of

orchiectomy and estrogen therapy are in some instances due to extragonadal production of androgens. It was with this idea in mind that the present study was undertaken. The hormonal influences on cancer are at times very dramatic but are also disappointing. Perhaps this failure to respond is due to a combination of factors (vide supra); for example, host resistance as well as stimulation of sites (pituitary) other than the primary lesion, which indirectly adversely influence the results. Anti-androgenic treatment has been shown to stimulate endogenous androgen production. This observation has been noted in a limited number of cases in which effective suppression of endogenous androgen production by the administration of similar steroid hormones acts through inhibition of androgen stimulating hormones of the hypophysis.<sup>24</sup> A temporary stimulation of tumor growth may occur with the administration of androgens but with cessation of therapy the endogenous secretion may be reduced. These experiments point to the possibility of ultimate and complete androgen withdrawal by hypophysectomy. This question, however, is not within the scope of this paper and cannot be answered at the present time. However, such investigations are of great interest and may be of considerable significance as the number of studies is increased.<sup>14</sup>

#### SUMMARY AND CONCLUSIONS

Three cases of advanced prostatic cancer were subjected to bilateral adrenalectomy following their failure to respond to or after having escaped from the effects of conventional anti-androgenic therapy. Case 1 underwent bilateral adrenalectomy 2 months after escape from conventional therapy, which was 19 months after the diagnosis had been made originally. He is living and asymptomatic at the present time, nine months after total adrenalectomy. Case 2 underwent adrenalectomy 30 months after diagnosis and radical perineal prostatectomy and 17 months after escape from the effects of orchiectomy. He survived 4 months following adrenalectomy but succumbed to cardiac failure. He showed moderate subjective and objective improvement. Case 3 underwent adrenalectomy 16 months after diagnosis and 10 months after escape from orchiectomy and estrogenic therapy. He survived 4 months but succumbed to carcinomatosis and showed no improvement.

Variations in response to adrenalectomy are possibly on the same basis as variations in response to other forms of anti-androgenic therapy. Only through careful evaluation of a large number of cases, performed in different stages of the disease, may it be determined when the procedure may prove to be most useful. The failures occurred in the two patients with undifferentiated prostatic carcinoma. The patient with a well differentiated adenocarcinoma responded well to adrenalectomy.

Improvement in surgical technique and the availability of substitution adrenal therapy justify total adrenalectomy in selected cases of prostatic cancer. There were no operative deaths. The striking and persistent improvement in one of the three cases is sufficient stimulus to warrant further investigation.

2515 Habersham St., Savannah, Ga.

<sup>24</sup> Brendler, H., Chase, W. E. and Scott, W. W.: Arch. Surg., 61: 433, 1950.

## "ADENOMATOID" TUMOR OF THE TUNICA VAGINALIS

S. S. AMBROSE, JR.

*From the Department of Urology of the U. S. Naval Hospital, Camp Lejeune, N. C.*

The designation *adenomatoid tumors* was proposed by Golden and Ash<sup>1</sup> in 1945, for a group of rare, benign tumors limited to the epididymis, testicular tunics, and serosal surface of the Fallopian tube; and it was noted that the name had the advantage "of being morphologically correct and genetically neutral". Their impression that the tumor is probably of epithelial origin is supported by others,<sup>2, 3, 4, 5, 6, 7, 8, 14</sup> but the term *adenomatoid tumors* properly leaves much room for further discussion of the genesis of these neoplasms.

This case is presented because of several features that strongly support the conclusion of Evans,<sup>9</sup> which is supported by others,<sup>10, 11, 12, 15, 16</sup> that these tumors are mesothelial in origin.

### CASE REPORT

A 37 year old white man was admitted to the U. S. Naval Hospital, Camp Lejeune, N. C. on May 27, 1951, with the history of a slowly growing, painless, slightly tender mass in the right hemi-scrotum of 3 years known duration. There was no history of local injury preceding the appearance of the lesion, and there was no history of any other genito-urinary tract disorder.

General physical examination was entirely within normal limits except for a 3 by 3 by 0.5 per cm. discoid, firm, slightly tender mass lying adjacent to the antero-medial aspect of the left testicle. The lesion could be moved freely over the surface of the testicle indicating probable fixation to the parietal tunica vaginalis. The left epididymis was completely separate from this mass.

Laboratory tests including hemoglobin, white blood cell count, differential count, urinalysis, and serological test for syphilis were all within normal limits.

The left tunica vaginalis was entered through a midline scrotal incision. The exposed testicle and epididymis appeared to be normal. On the parietal surface of the tunica was a slightly raised discoid, firm, almost cartilaginous, sharply

Accepted for publication July 30, 1952.

The statements and conclusions published here are those of the author and do not necessarily reflect the opinion or the policy of the Bureau of Medicine and Surgery of the U. S. Navy.

<sup>1</sup> Golden, Alfred and Ash, J. E.: *Am. J. Path.*, **25**: 63, 1945.

<sup>2</sup> Blumer, C. E. M. and Edwards, J. L.: *Brit. J. Surg.*, **29**: 263, 1942.

<sup>3</sup> Gordon-Taylor, G. and Ommaney-Davis, C.: *Brit. J. Surg.*, **29**: 260, 1941-42.

<sup>4</sup> Codnere, J. T. and Flynn, J. E.: *J. Urol.*, **56**: 449, 1946.

<sup>5</sup> Thompson, G. J.: *Surg., Gynec. & Obst.*, **62**: 712, 1936.

<sup>6</sup> Hinman, F. and Gibson, T. E.: *Arch. Surg.*, **8**: 100, 1924.

<sup>7</sup> Sakaguchi, Y.: *Frankfurt. Ztschr. f. Path.*, **18**: 379, 1915-16.

<sup>8</sup> Falconer, B.: *Ztschr. f. Krebsforsch.*, **48**: 243, 1938.

<sup>9</sup> Evans, Newton: *J. Urol.*, **50**: 255, 1943.

<sup>10</sup> Evans, Newton: *Am. J. Path.*, **19**: 461, 1943.

<sup>11</sup> Masson, P. and Riopelle, J. L.: *Rev. Canad. Biol.*, **1**: 720, 1942.

<sup>12</sup> Lee, M. J., Dockerty, M. B., Thompson, G. J. and Waugh, J. M.: *Surg., Gynec. & Obst.*, **91**: 221, 1950.

<sup>13</sup> Schiller, W.: *Arch. Path.*, **33**: 443, 1942.

<sup>14</sup> Sworn, B. R., Marshall, F. W. and Edwards, J. L.: *Brit. J. Surg.*, **33**: 375, 1946.

<sup>15</sup> Robinson, J. N.: *Brit. J. Urol.*, **17**: 68, 1945.

<sup>16</sup> Glaser, S.: *Brit. J. Urol.*, **22**: 178, 1950.

circumscribed tumor mass. The remainder of the tunica appeared to be normal. The mass was excised with a margin of normal tissue and the scrotum closed.

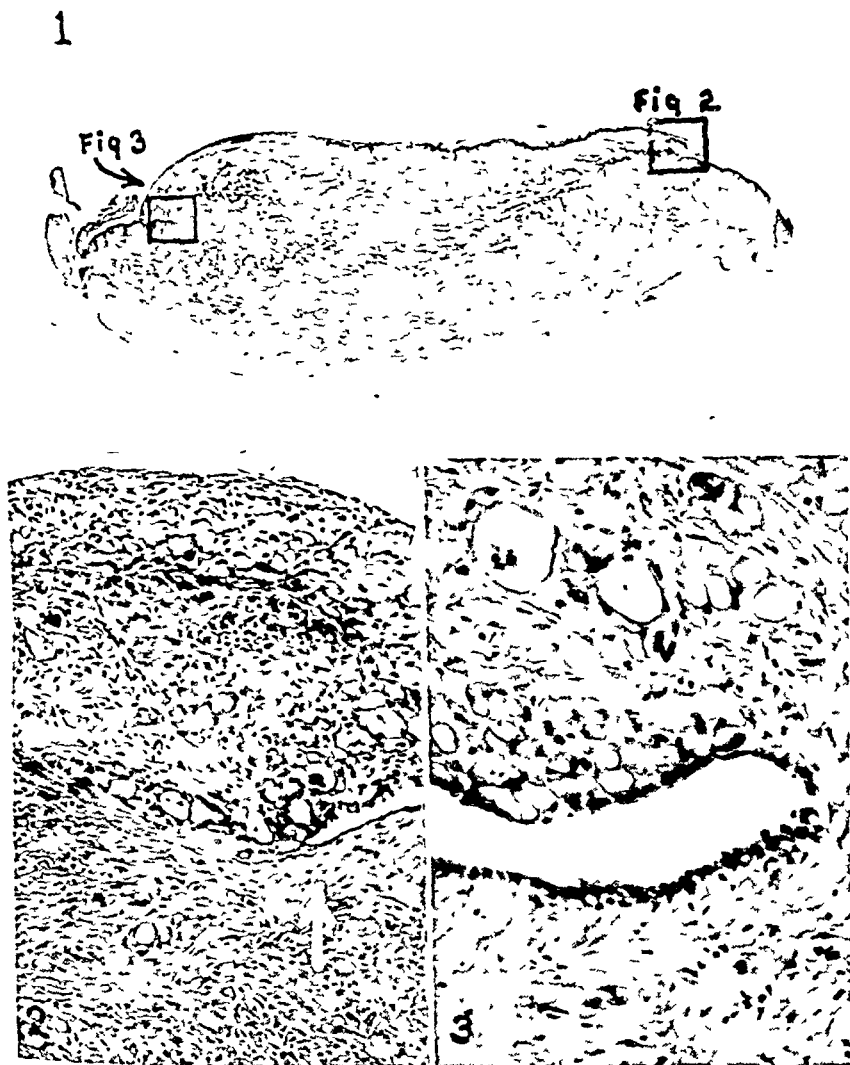


FIG. 1. 1, cross section of entire tumor. Superior surface presented in space of tunica vaginalis. Lateral edges represent margin of normal serosa excised. 2, higher magnification reveals junction of normal serosal cells and large eosinophilic, vacuolated cells typical of this tumor. 3, junction of normal serosa and tumor cells at opposite border of tumor is revealed here. Apparent transition of normal serosal mesothelium to cells typical of this tumor.

Recovery was uneventful and the patient was returned to duty one week after operation. There has been no evidence of recurrence during the past year.

The specimen was sent to the U S Naval Hospital, Bethesda, Md, for examination, and the pathological diagnosis was "adenomatoid tumor of the tunica vaginalis." See figure 1.

## DISCUSSION

The tumor presented here is of more than passing interest because of its anatomical position on the parietal tunica vaginalis opposite the testicle and its apparent continuity with the normal serosa of the tunica. From its position on the parietal tunica, there were at least 2 cm. of serosal surface between the tumor and testicle or epididymis in any direction. This fact is, I think, suggestive evidence against the theories of origin from misplaced embryonic genital ridge, mesonephros, or from epithelial elements of the epididymis.<sup>3, 4, 13</sup>

Histologically (fig. 1), the picture is that of a well circumscribed tumor separated from the underlying scrotal tunics by a thin fibrous capsule and presenting a slightly raised surface within the tunica vaginalis sac. The free surface is covered in part by flattened mesothelial cells, but in other parts consist of a deep layer of large vacuolated cells. The dominant features are the dense fibromuscular stroma and the numerous gland-like spaces of varying size and contour scattered in irregular pattern through this stroma. These spaces vary in size from large vacuoles to spaces that are lined with cells that vary from flat fusiform or squamous to cuboidal in shape. Many of the larger spaces appear to be single vacuoles that are distorting surrounding cells by pressure. There are many solid strands of large, irregular, vaguely outlined cells with eosinophilic cytoplasm that is finely granular and not infrequently contain clear, small vacuoles. The nuclei are large, round to oval, with thin chromatin network and usually present a prominent nucleolus. Mitosis is very rare. The gland-like structures present no basement membrane, and there are no cilia. Mucicarmine stains were negative for mucin in the alveolar spaces. There appears to be a transition of normal serosal mesothelial cells of the surrounding tunica vaginalis into cells typical of this neoplasm as can be seen in the photomicrographs taken at the slightly raised lateral borders of this tumor.

## CONCLUSION

It is believed that the position of this tumor on the parietal tunica and the apparent transition of normal serosal cells into tumor cells strongly support the hypothesis that "adenomatoid tumors" are histogenetically derived from the mesothelial cells of the serosa of the tunica vaginalis.

## FURADANTIN IN INFECTIONS OF THE GENITO-URINARY TRACT

CHARLES M. NORFLEET, JR., PARKER R. BEAMER AND HARRY M. CARPENTER

*From the Department of Surgery, Division of Urology, and the Department of Microbiology and Immunology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.*

In 1944, Dodd and Stillman<sup>1</sup> found that the addition of a 5-nitro group caused a number of furan compounds to become antibacterial. Furacin,<sup>®2</sup> a product of this work, was used in chronically infected war wounds in 1945.<sup>3</sup> Since then it has been accorded wide usage. Green and Mudd<sup>4</sup> obtained organisms which had developed resistance to sulfonamides, penicillin, and streptomycin. These, as well as their parent susceptible strains, were tested in parallel for sensitivity to Furacin. No differences could be demonstrated in these paired strains in their susceptibilities to Furacin. A recent report by Sweetser and Harrison<sup>5</sup> indicates its value in urethrotigonitis.

Further work with the nitrofurans has produced Furadantin, brand of nitrofurantoin, N-(5-nitro-2-furfurylidene)-1-aminohydantoin (fig. 1). Its oral administration, tolerance and effectiveness in the therapy of genitourinary tract infections in the human are the subjects of the investigation reported here.

### PHARMACOLOGY

In preliminary work at Eaton Laboratories, toxicity studies with animals indicated a wide margin of safety with this drug. The L.D. 50 in mice was found to be 895 mg./kg. Prolonged dosage in rats, higher than can be tolerated by the human, produces depression of spermatogenesis. This is a reversible process, disappearing after cessation of therapy. No other toxic manifestations have been found.

Several patients with known sensitivity to Furacin have been patch tested and the majority were found not sensitive to Furadantin.<sup>6</sup>

Urinary excretion studies at Eaton Laboratories showed that 30 to 40 per cent of orally administered Furadantin was excreted in the urine of albino rats. The drug was given to four normal human males, and an average of 44 per cent was excreted in 8 hours. The major portion of this was excreted in 4 hours.

This investigation was supported in part by a grant from the Eaton Laboratories, Inc., Norwich, N. Y.

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 3, 1952.

<sup>1</sup>Dodd, M. C. and Stillman, W. B.: The in vitro bacteriostatic action of some simple furan derivatives. *J. Pharmac. & Exp. Therapeut.*, **82**: 11, 1944.

<sup>2</sup>Daily, L. E.: The nitrofurans. *New York State J. Med.*, **48**: 1386, 1948.

<sup>3</sup>Synder, M. L., Kiehn, C. L. and Christopherson, J. W.: Effectiveness of a nitrofuran in the treatment of infected wounds. *Mil. Surg.*, **97**: 380, 1945.

<sup>4</sup>Green, M. N. and Mudd, S.: The susceptibility to furacin of bacterial strains resistant to sulfonamides or antibiotics. *Proc. Soc. Exp. Biol. & Med.*, **64**: 57, 1947.

<sup>5</sup>Sweetser, T. H., Jr. and Harrison, C. H., Jr.: Nitrofurazone in treatment of urethrotigonitis. *J. Urol.*, **65**: 684, 1951.

<sup>6</sup>Daily, L. E.: Personal communication.



In our series, the only side effects have been slight gastric uneasiness to nausea in 12 per cent and vomiting in 2 per cent of patients. Both ceased promptly upon withdrawal of the drug. This is actually a safety factor, for any marked overdose produces vomiting.

The arbitrary figure of between 7 and 9 mg./kg./day was selected for these patients. It was postulated that this would be well above the therapeutic range, but also that it would approach the level of nausea. With but rare exception, this dosage schedule was well tolerated. Each patient took the drug 4 times a day for 4 or 5 days. Several repeated therapy for 4 days, and two received Furadantin in interrupted courses for as long as a year.

#### CLINICAL MANAGEMENT

Fifty ambulatory patients, having either acute or chronic genito-urinary tract infection, were treated. In most instances, the patients were seen at weekly in-

#### Furadantin

N-(5-nitro-2-furfurylidene)-1-aminohydantoin

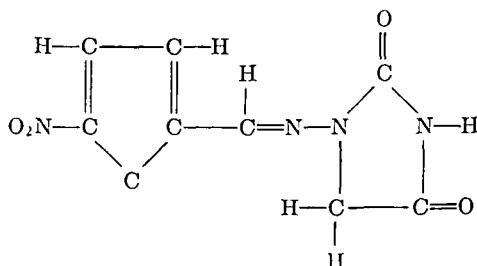


FIG. 1

tervals. Microscopic urinalyses and urine cultures were performed initially as described later. In the group with prostatic infection, the prostatic secretion was examined microscopically and in some instances cultured. This was repeated 2 to 3 days after cessation of therapy and again in 9 to 10 days. In 21 patients pre- and post-treatment, a complete blood count was obtained. No appreciable changes were noted in the blood counts.

No other therapeutic measures were used in the treatment of pyelonephritis or cystitis. The patients who had prostatitis subsequently were given prostatic massage.

#### BACTERIOLOGIC IDENTIFICATION AND SENSITIVITY STUDIES

Catheterized or "clean voided" specimens of urine, or prostatic secretion, were collected aseptically in sterile containers and examined immediately. Smears were prepared for microscopic examination and stained according to a modified Gram procedure in order to determine the morphologic types present. Ordinarily, specimens were streaked on blood agar plates (tryptose agar plus defibrinated human blood in a concentration of five per cent) and MacConkey's agar plates. In addition, 3 to 5 ml., or as large an aliquot as possible, were added to thioglycollate broth. After incubating at 37C for 24 hours, single colony isolations were

prepared from the plate cultures by transfer to brain-heart infusion broth, and the thioglycollate culture was examined to detect growth of organisms which may not have grown in plate cultures incubated aerobically. In this series of studies, however, no anaerobic or micro-aerophilic species were encountered. Additional media and techniques were employed whenever indicated by the microscopic findings. Following isolation, organisms were studied in various differential media in order to make specific identifications on the bases of biochemical characteristics. Serologic studies were performed whenever indicated. *Bergey's Manual of Determinative Bacteriology* (sixth edition) was used as the guide for classification.

For the purpose of determining susceptibility of organisms to Furadantin *in vitro*, the drug was dissolved in polyethylene glycol 300, in a concentration of 0.5 per cent. This procedure makes it possible to study the activity of Furadantin in amounts exceeding those which are soluble in broth and are more nearly like the levels attained in urine. Serially increased concentrations of Furadantin in culture medium were prepared immediately before testing by the addition of 0.1, 0.2, 0.4, and 0.6 ml. amounts of Furadantin solution (as above) to tubes containing, respectively, 9.8, 9.7, 9.5, and 9.3 ml. of sterile brain-heart infusion broth. These dilutions provide final concentrations of 5, 10, 20, and 30 mg. of Furadantin per 100 ml., respectively. A fifth tube in the series, containing 9.3 ml. of broth to which 0.6 ml. of polyethylene glycol 300 (without Furadantin) was added, constituted the control. One-tenth milliliter of a young (10 to 12 hours) culture of the organism to be tested was added to all tubes, which were then incubated at 37C. Each series of tubes was examined macroscopically for evidence of growth at 24 hours and again at 48 hours. In those instances where growth was not apparent, 0.1 ml. of the contents of the tube was removed and transferred to 9.9 ml. of sterile brain-heart infusion broth. These "check" tubes were incubated in the same way and examined for evidence of growth at 24 hours and again at 96 hours following inoculation. If the inocula from tubes showing no growth in the first series subsequently produced growth in the second series, the action of Furadantin, in that particular concentration, was rated as "inhibitory" (table 1\*). In instances where no growth was detected in "check" tubes after 96 hours of incubation, the activity of the drug was designated as "bactericidal" (table 1).

Results of the *in vitro* sensitivity studies on 55 strains of organisms isolated from acute and chronic infections of the genito-urinary tract may be summarized as follows:

- 1) *Streptococcus pyogenes*: Only strain isolated was inhibited and killed by Furadantin in a concentration of 5 mg. per 100 ml.
- 2) *Micrococcus pyogenes* var. *aureus* and *albus*: Six of the seven isolates were killed by concentrations of 20 mg. per 100 ml. or less; definite inhibitory effect was demonstrated against all strains at levels of 10 mg. per 100 ml. or less.
- 3) *Escherichia coli*: Sixteen of the 19 isolates were killed by concentrations of 20 mg. per 100 ml. or less; one was killed by 30 mg. per 100 ml., and the re-

\* The tables will be found in the authors' reprints, and also in the authors' paper in the 1952 Transactions of the Southeastern Section, American Urological Association.

maining two were resistant to the drug; inhibitory effect was demonstrated against sixteen strains at levels of 10 mg. per 100 ml. or less, and one strain was inhibited by 20 mg. per 100 ml.

4) *Aerobacter aerogenes*: Four of the 9 strains isolated were killed by concentration of 20 mg. per 100 ml. or less, one was killed by 30 mg. per 100 ml., and four were resistant; inhibitory effect was demonstrated against five strains at levels of 10 mg. per 100 ml. or less.

5) *Paracolobactrum* sp. (paracolon): Only two of five isolates were killed by 20 mg. per 100 ml. or less, and the other three were resistant; two of the latter were not even inhibited by the drug, but the other was inhibited by 10 mg. per 100 ml.

6) *Streptococcus* sp., alpha hemolytic type: Only two strains were encountered; one was completely resistant to the drug, and, although no bactericidal action was noted, the other was inhibited by 30 mg. per 100 ml.

7) Two strains of *Alcaligenes faecalis*, four *Proteus* species and five strains of *Pseudomonas aeruginosa* were isolated and all were resistant; Furadantin in a concentration of 30 mg. per 100 ml. apparently had no inhibitory effect on the multiplication of these organisms in vitro.

8) From one patient a *Corynebacterium* sp. (diphtheroid) was the only organism isolated repeatedly, and, although its significance as a causal agent is difficult of assessment, this strain was resistant to Furadantin with a concentration of 30 mg. per 100 ml.

It should be noted that "inhibitory effect," as used in the foregoing summary, refers to failure of the organism to reproduce and multiply, as determined roughly by careful visual examination of cultures. Also, it should be noted that the figures in the following section (Results), summarizing clinical observations, are based on results of cultures made before and during therapy with Furadantin. Therefore, the total numbers do not agree exactly with those in the above summary because a) some organisms cited on p. 30 were isolated prior to the time sensitivity studies were begun, and b) re-isolates of the same species are enumerated separately in the above summary if there was a variation in the results of the sensitivity tests.

## RESULTS (TABLE 2\*)

The 2 patients with acute pyelonephritis noted prompt symptomatic improvement, and within 8 days the urine was microscopically negative and no growth was noted in cultures. They received Furadantin 4 and 6 days respectively.

Only one of the 25 patients having acute cystitis required a second four-day course of therapy. Fifteen of these had negative urine and complete symptomatic and bacteriologic cures. Five were asymptomatic and had negative microscopic urine but showed a positive culture. One was asymptomatic; the urine was negative but the culture was lost and therefore presumed positive. Two had negative urine and culture but complained of slight bladder discomfort. One was im-

\* The tables will be found in the authors' reprints and also the authors' paper in the 1952 Transactions of the Southeastern Section, American Urological Association.

proved but pyuria persisted until a small unrecognized calculus was passed. One patient experienced no improvement whatsoever in urinalysis or culture. She had no discomfort from this symptomless pyuria.

Six patients had complained of mild to moderate bladder symptoms for more than 2 months and were diagnosed as chronic cystitis. One had an infected hydro-nephrosis and showed no improvement with Furadantin therapy. Following nephrectomy, the cystitis disappeared. Three patients noted slight improvement, but microscopic urine and culture remained unchanged. One patient had complete relief, the microscopic urine was negative, but the culture remained positive. The sixth patient has taken Furadantin from 3 to 5 days out of every 3 weeks for 1 year. Her urine became almost free of pus and at times completely free. The culture has been negative on several occasions and consistently, the bladder symptoms have been controlled. The complicating factor has been a low grade chronic pyelonephritis and a mild neurogenic bladder. Prior to Furadantin therapy, she had taken a total of one thousand capsules of Chloromycetin.

Of 15 patients with prostatitis, two were arbitrarily classified as acute. One had severe infection and marked symptoms 8 weeks post-prostatectomy. After 9 days of Furadantin, his symptoms had disappeared and his urine was clear. The second patient had chills, fever, prostatic pain, and pyuria. Although his culture remained positive, his symptoms disappeared and the urine was negative in one week. Therapy was continued on a decreasing dosage schedule over a 6 week period.

The use of the term improved must be qualified when referring to chronic prostatitis. In this report, it means reduction or disappearance of discomfort and/or cessation of prostaticorrhea. It is significant only because all of these 13 patients had previously received the usual prostatic massage, urethral sounds, sitz baths, chemotherapy, and antibiotics with little or no improvement. Only five received a single course of Furadantin, the others receiving two or more courses. One patient was not improved. Twelve were improved. All continued to have an increased number of white blood cells in the prostatic secretion.

One patient having an abacterial urethritis and conjunctivitis, but without arthritic manifestations, had previously received two antibiotics, and two sulfonamide preparations without improvement. An 8 day course of Furadantin did not alter his symptoms.

Furadantin was given for 12 days, before tubercle bacilli were found, to a young woman who had marked dysuria and pyuria. Although the pyuria was unchanged, her dysuria was improved from 50 to 75 per cent.

A list of 36 organisms eradicated from the genito-urinary tract, as demonstrated by culture, is found in table 3. Some of these occurred as mixed infections. The following ratios indicate the number eradicated as compared with the total number of strains isolated: *Escherichia coli*, 16:22; *Paracolobactrum* sp. (paracolon), 4:5; *Aerobacter aerogenes*, 4:6; *Proteus* sp., 3:5; *Micrococcus pyogenes* var. *aureus* and *albus*, 3:7; *Streptococcus* sp., alpha-hemolytic type, 2:2; *Streptococcus pyogenes*, 1:1; *Corynebacterium* sp., (diphtheroids), 1:4; *Alcaligenes faecalis*, 1:2; *Pseudomonas aeruginosa*, 1:3.

## COMMENT

Despite the availability of numerous antibiotics and sulfonamide compounds for use in the treatment of genito-urinary infections, we believe there is need for others. Furadantin is an effective broad-spectrum chemotherapeutic agent and we have found it to give gratifying results. While nausea has been experienced with high dosage, it did not require the cessation of therapy. Reducing the dosage has lowered the incidence of nausea. No harmful effects have been noted. Several patients reported marked improvement in symptoms in from 24 to 48 hours after taking Furadantin.

The limitations of the bacteriologic method employed for determining the antibacterial action of Furadantin are such that the figures tabulated should not be regarded as specific, absolute values because they are only relative values which indicate 1) marked susceptibility, 2) moderate susceptibility, or 3) resistance to the action of Furadantin *in vitro*, under the specific conditions of the test. For example, certain modifications in procedure often produce values which are at variance with those tabulated. In general, however, the trends shown for various strains are significant. Sensitivity values such as those tabulated usually imply what may be expected clinically in the chemotherapy of an infection. However, there are occasional exceptions which are probably the result of factors which cannot be measured by laboratory procedure, as shown by the clinical effectiveness in three of the five patients with *Proteus* infections, one with *Alcaligenes*, and one having *Pseudomonas* infection.

## SUMMARY

Furadantin, a new nitrofuran, was administered systemically by the oral route to 50 ambulatory patients having acute or chronic genito-urinary tract infections.

The results of this study indicate it to be a safe and effective agent having a broad antibacterial spectrum. No case of sensitization has occurred.

In a few instances, *in vitro* tests indicated apparent resistance of the bacteria, but negative cultures and absence of symptoms following treatment affirmed the clinical effectiveness of Furadantin. Only four of 50 patients failed to show improvement.

## NOTE

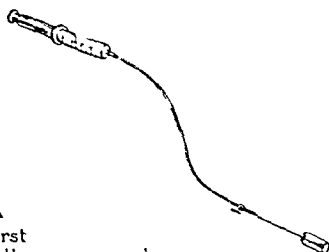
An additional 22 patients, not included in the context or tables, have been treated with equally satisfactory results.

## A SIMPLE INJECTOR FOR AORTOGRAPHY AND INTRAVENOUS ANGIOGRAPHY

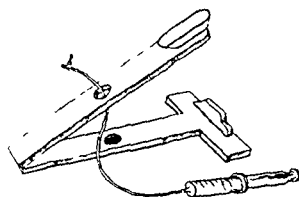
FRANK HINMAN, JR.

*From the Department of Surgery, Division of Urology, University of California School of Medicine, San Francisco, Calif.*

We needed a simple fool-proof device to inject concentrated, viscid urokon® or diodrast® for aortography and intravenous angiography. Hand injection was too slow to get an effective bolus of dye in the aorta unless two needles were



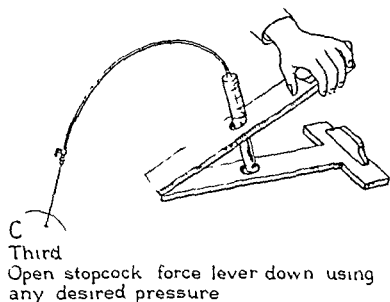
A  
First  
Fill syringe and pressure  
tubing, close stopcock



B  
Second  
Insert syringe through opening and  
attach to needle in vein



FIG. 1



C  
Third  
Open stopcock, force lever down using  
any desired pressure

FIG. 2

FIG. 1. Photograph of apparatus ready for use, showing: 1) 50 cc syringe, 2) polyethylene tubing swedged and bound to adaptor and two-way stopcock, 3) device consisting of two flat boards hinged proximally. Hole in upper board is too small to allow passage of flange of syringe barrel.

FIG. 2. A, syringe is filled and stopcock closed. B, tubing and most of syringe barrel is threaded up through hole in upper board. C, after insertion of needle into aorta or brachial vein, stopcock is attached, opened and strong leverage exerted on handle to force dye into vessel.

Accepted for publication July 30, 1952.

inserted or unless a very large bore needle was used. A home-made wooden lever was therefore constructed (fig. 1) which allows tactile control during injection but increases the injection rate almost threefold (table 1).

TABLE 1. *Injection with full manual pressure, 18 gauge needle, wrokon*

---

|                     |
|---------------------|
| By hand—8 seconds   |
| By device—3 seconds |

---

The diagrams show the steps of operation (fig. 2, *A*, *B*, and *C*).

We have tested this device experimentally in dogs as well as clinically, and found the only difficulty is occasional crumbling of the solid end of the plunger with too forceful injection. This occurrence, however, does not interfere with the injection and can be reduced by padding the socket in the lower board.

*348 Post St., San Francisco 8, Calif.*

## A TECHNIQUE FOR REPLACING A CATHETER SPLINT FOLLOWING ACCIDENTAL OR PREMATURE REMOVAL IN INTUBATED URETEROTOMY

J. ROBERT RINKER

*From the Department of Urology, Medical College of Georgia, Augusta, Ga.*

An open defect in the wall of the ureter (fig. 1) may be treated successfully by intubation, providing the splinting catheter remains in the ureter for an adequate



FIG. 1

period of time. Premature removal of the splinting catheter soon after operation may jeopardize the success of the procedure by allowing a stricture to form at the site of the defect instead of a lumen of adequate caliber. Faced with the critical situation of accidental or premature removal, one may try to maintain intubation by retrograde catheterization. This may be fraught with difficulties; first, it may not be possible to pass the defect in the ureter with a catheter of adequate size;

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 5, 1952.

A motion picture illustrating the technique was shown at annual meeting, American Urological Association, Atlantic City, N. J., June 24, 1952.



particularly, if it is soon after surgery and the edges of the gap are open. Second, retrograde intubation is less satisfactory than splinting through a nephrostomy or pyelostomy as the ureteral catheter tends to slip down the ureter adding uncertainty as to whether the desired area is being intubated as it should. This is particularly true in the ambulatory patient; furthermore, the ureteral catheter inlying in the urethra adds to the discomfort of the patient. If accidental or premature removal occurs late in the convalescent period one may try to carry the patient along by retrograde intubation to a successful termination, but if the

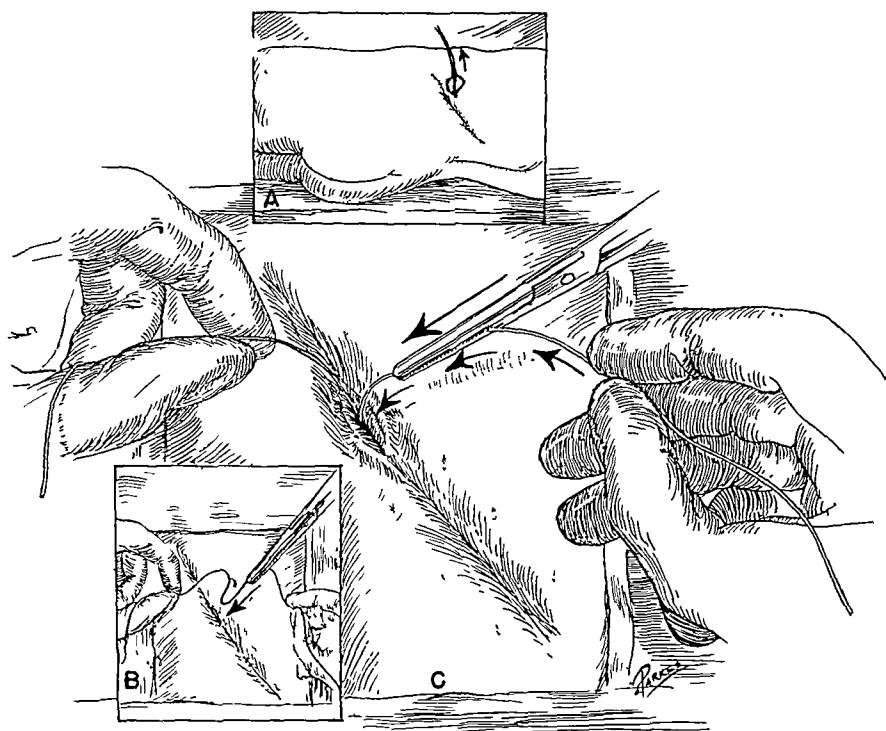


FIG. 2

accident occurs soon after the operation, it may mean embarking on a series of cystoscopies and ureteral catheterizations with uncertain outcome. If several weeks of intubation are still necessary, it is better to replace the splint through the nephrostomy or pyelostomy. To reoperate upon the patient and replace the catheter is an unhappy thought; although in retrospect I have wished that I had elected to do it on a few occasions.

One may ask, why not use the Cummings or McIver catheter with less likelihood of this difficulty? In spite of occasional difficulties there are advantages in using a separate nephrostomy tube and ureteral splint. The first being that either tube may be removed at a different time. It is also well to move the ureteral splint a little at intervals at the end of the splinting catheter may cause some stricturing in the ureter, if it remains in one place for a long period of time. Moving the splint

and use of Suby's solution might prevent difficulty in removing a rubber catheter splint, as encountered by Baker on two occasions. He found the splints plastered to the ureters and had to reoperate on the patients to remove them.

On an occasion 3 years ago, I was faced with the dilemma of having a ureteral splint come out on the seventh postoperative day. The stitch holding the catheter was removed in error under circumstances I was unable to anticipate. In this

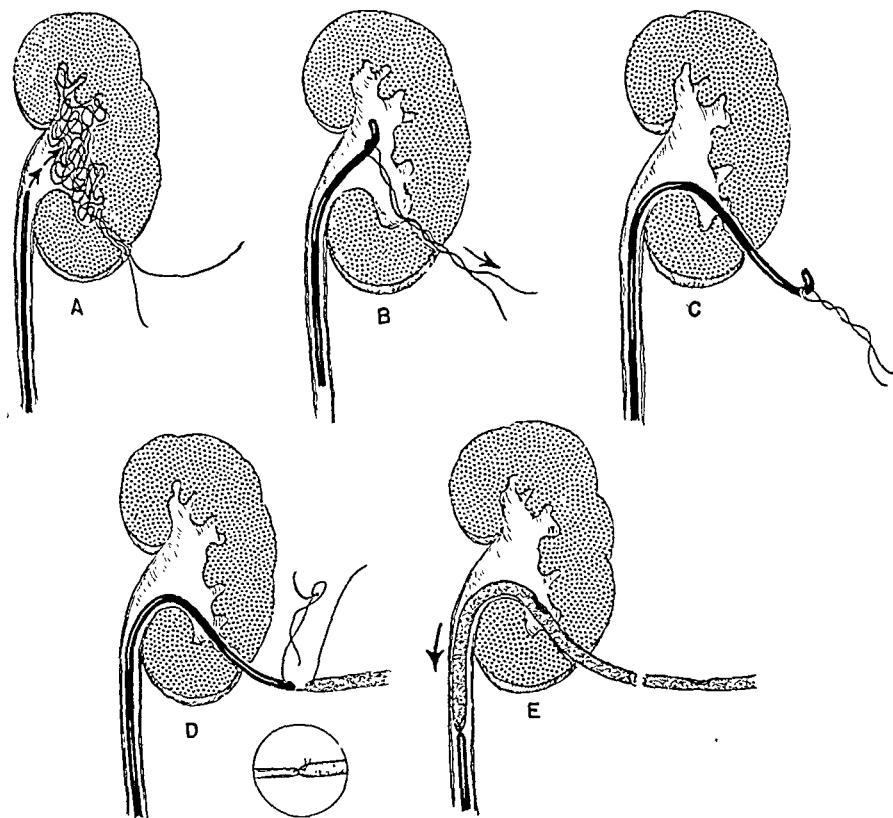


FIG. 3

patient it seemed that the operation would surely result in failure unless the splint was replaced. I conceived this simple way to replace it and it worked with the greatest of ease. On one occasion since, I used it on a similar patient on the eighth postoperative day and it stood me in good stead again. This time we made a motion picture of the procedure and I am passing it on to you.

#### PROCEDURE

A ureteral catheter is passed retrograde to the renal pelvis (this should be done as soon as possible after the splinting catheter comes out) and the nephrostomy tube is removed (fig. 2, A). Starting with a loop of 30 g. steel wire, 30 inches of the wire is fed into the renal pelvis through the nephrostomy wound forming a network of wire coils (fig. 3, A). The ureteral catheter is then pushed into the coils

and the wire retrieved, delivering the tip of the ureteral catheter (3, C). A fine plain catgut stitch is used to attach the end of the ureteral catheter to the splinting catheter (fig. 3, D). Traction on the ureteral catheter pulls the splinting catheter into place (fig. 3, E). In two or three days the catgut disintegrates and the ureteral catheter comes away. Anesthesia was not necessary.

I wish to thank Mr. O. A. Parkes, Chairman of the School of Medical Illustration, Medical College of Georgia, for the drawings.

*406 University Hospital, Augusta, Ga.*

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BAKER, W. J.: Personal communication.

## MEATOTOMY ELECTRODE

KENNETH T. ROWE

As urologists, we frequently have difficult problems to master. I can think of no more aggravating condition than a ureteral stone engaged in the terminal portion of the ureter, a size which should pass if the terminal ureteral orifice and intravesical segment of the ureter could be enlarged sufficiently. We have all experienced this relatively common problem with a stone shown on x-ray in the terminal ureter approximately the size of a bean, and on cystoscopy find to our disappointment the ureteral orifice would barely accommodate a 6F catheter. Anatomically, the terminal 2-3 cm. of the ureter passes obliquely through the bladder wall and in many cases at least 2 cm. of the ureter lies completely within the bladder covered only by the mucosal lining plus the ureteral wall. It is in these cases of blockage that we find it extremely difficult to get adequate dilatation since filiform type catheters will become obstructed by the engaged calculus



FIG. 1. Ureteral meatotomy electrode

and dilatation is prevented. We then try ureteral scissors and various other gadgets generally ending up with a hemorrhagic field and the procedure is necessarily postponed. Some years ago when one of these bean sized calculi became engaged in this terminal, intravesical portion I used the cutting McCarthy loop and completely excised the top of the bulging ureter. The calculus then dropped into the bladder and our problem was solved. Several other urologists have reported such procedures with equal success.

The problem still remained as to how best to handle the case where the stone becomes engaged in the terminal ureter before it penetrated the oblique mucosal layers of the bladder. It is apparent that the ureter has dilated sufficiently through its entirety to allow the stone to pass from the kidney down to the bladder segment. With this in mind I developed the instrument presented today which can be used with the ordinary McCarthy resectoscope (fig. 1). The insulated filiform tip of the instrument passes in the ureteral orifice and is advanced to the area where the bare cutting wire engages the ureteral mucosa. As the instrument is now carefully advanced 1½ cm., the bladder portion of the ureter is completely opened and converted into a large trough. No bleeding should occur as the area is fulgurated during the cutting operation and the landmarks are well defined.

I have found that there are two helpful procedures that should be adhered to:  
1) When possible a catheter, even though it is small, should be passed above the stone up to the kidney for drainage before the meatotomy is attempted. If the

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla., April 4, 1952.

ureteral orifice is of such small diameter it would not conveniently accommodate the small catheter plus the meatotomy tip, the catheter may be gently withdrawn at the time we are ready to engage the electrode. The catheter in place is a helpful landmark when using the McCarthy foroblique lens system. 2) It is important to avoid force or pressure during the cutting incision; it is important to gently advance the loop in the direction of the ureter without distortion.

Whenever possible I recommend leaving a ureteral catheter up to the kidney after this meatotomy. This gives adequate drainage to the obstructed kidney and usually the normal peristalsis will bring the catheter down a few centimeters and the stone will drop into the bladder or be expelled shortly after removing the ureteral catheter.

*Hornell, N. Y.*

## A NEW FILIFORM COUPLING

WILFORD A. H. COUNCILL, JR.

*From the Department of Urology, University of Virginia Hospital, Charlottesville, Va.*

New ideas for improvement of instruments and methods in urology are necessary if progress is to be made. We should like to present a new concept in filiform construction and application which we have found to be of value in our clinic.

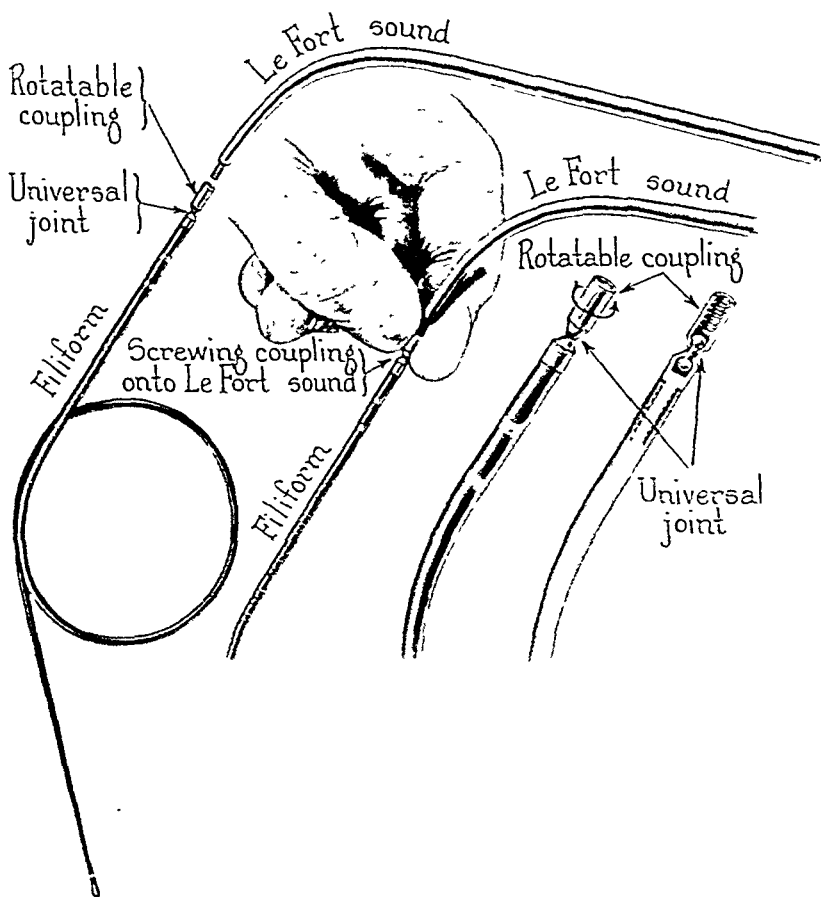


FIG. 1

The present filiform and Le Fort following sound are indispensable instruments in urological office practice, but the attachment of one to the other preliminary to urethral dilatation leaves much to be desired. The usual cranking ritual used to thread the Le Fort sound into the filiform is an awkward maneuver. Furthermore, unless patience and care are exercised the threads are easily stripped.

Accepted for publication September 15, 1952

rendering the filiform useless. Movement of the entire arm and shoulder girdle muscles is necessary for this simple procedure.

After experiencing this time-consuming and clumsy manipulation on numerous occasions, the writer was prompted to devise a new filiform fitted with a universal joint. The application of such a joint enables the operator to thread one instrument to the other in a quick and efficient manner. The maneuver is simple and merely utilizes the movement of one thumb and index finger.

The filiform is inserted into the urethra in the usual manner and held in the left hand between the thumb and index fingers (fig. 1). The follower is then placed to engage the threads of the filiform and the coupling screwed counterclockwise onto the follower by rolling between thumb and index finger. The combination is then ready for passage into the urethra.

The new coupling provides for more accurate alignment of the tiny threads by such finger-tip control, thus reducing the extensive moments of force exerted on the threads as a result of using the entire arm when attaching the conventional filiform tip. The stresses and strains on the threaded surfaces are therefore minimized and the span of usefulness of the filiform increased.

#### SUMMARY

A new filiform has been presented to facilitate the unwieldy procedure necessary to attach the following sounds or instruments.

The accompanying illustration by Mr. William P. Didusch serves to depict the instrument and its application. The writer wishes to express his thanks to Mr. Frederick J. Wallace of American Cystoscope Makers, Inc., for constructing the instrument.

## SURGERY OF THE ADRENAL GLAND FOR CUSHING'S SYNDROME

EUGENE F. POUTASSE (BY INVITATION) AND CHARLES C. HIGGINS

*From the Cleveland Clinic, Cleveland, O.*

Twenty years ago Harvey Cushing<sup>1</sup> described a group of patients with similar clinical manifestations whom he considered to have pituitary dysfunction. The disturbance was believed to be associated with an adenoma or basophilism of the pituitary gland. Little was then known of the function of the adrenal gland, but the past 20 years have seen great advancements in endocrinology and steroid chemistry. It is now generally believed that all patients with the clinical syndrome, which now bears Cushing's name, have hyperadrenocorticism.<sup>2</sup> In some instances this is caused by a tumor of the adrenal gland, but more often by hyperfunction of the adrenal cortex with or without hyperplasia. The stimulus causing this abnormal function is not understood. The term Cushing's disease is reserved for the few instances where a pituitary adenoma is demonstrable and the presumed cause of the hyperadrenocorticism.

Patients with Cushing's syndrome are easily recognized by the physician who has once had the opportunity to observe this anomaly and is familiar with the problem. They attract great interest because of the many physical and metabolic changes caused by the excess production of 11-oxysteroids by the adrenal cortex. The characteristic features of Cushing's syndrome are the round red face, hirsutism, obesity of the trunk and neck, purplish striae and thin, easily damaged skin, muscle weakness, amenorrhea or impotence, hypertension, diabetes, osteoporosis with back pain, pyelonephritis, and mental instability. Not all these features are present in every patient with the syndrome nor are they all necessary to make the diagnosis. Excess production of steroid metabolites resembling androgen occasionally occurs producing acceleration of growth in children, hirsutism, enlarged clitoris, increased musculature, and other manifestations known as the adrenogenital syndrome. It should be emphasized that symptoms and signs of adrenogenital syndrome and Cushing's syndrome can occur in the same patient, making the diagnosis difficult.

Cushing's syndrome is twice as common in women as in men; 19 out of 28 patients with this disease seen at the Cleveland Clinic since 1933 were women. The average age of all patients at the time the diagnosis was made is 30 years, the spread being from 18 months to 58 years of age. Unless a spontaneous remission occurs, the life span of these patients is greatly shortened. This is seen occasionally but is usually only temporary. By removing most or all of the adrenal glands the disease can be checked and the patient restored to a more normal state.

Hypersecretion of the adrenal 11-oxysteroids are believed to account for most

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 19, 1952.

<sup>1</sup> Cushing, H.: Bull. Johns Hopkins Hosp., 50: 137, 1932.

<sup>2</sup> Kepler, E. J. and Locke, W.: Chronic Adrenal Hyperfunction. Textbook of Endocrinology Edited by Williams, R. H., Philadelphia: W. B. Saunders Co., 1950, p. 180-248.



of the pathologic and physiologic changes in patients with Cushing's syndrome.<sup>3</sup> The two main steroid hormones involved are corticosterone and 17-hydroxycorticosterone (cpd F). After being metabolized in the body, these substances are excreted in the urine as 17-ketosteroids and corticoids. In men about three-fifths of the urinary 17-ketosteroids are derived from metabolites of the adrenal cortex, the remainder come from testis precursors.<sup>4</sup> In women practically all the 17-ketosteroids are derived from adrenal steroid metabolites. Many patients can be shown to have an excess of either or both of these excretory products by proper biochemical tests of the urine.<sup>5, 6</sup>

Most of the features of Cushing's syndrome can be produced by the prolonged administration of adrenocorticotrophic hormone,<sup>7</sup> which stimulates the adrenal gland, or large doses of cortisone (cpd E)<sup>3</sup> or 17-hydroxycorticosterone (cpd F).<sup>8</sup>

In our series of 28 patients with Cushing's syndrome, two were found to have a malignant adrenal cortical tumor. One was a 53 year old woman who had a

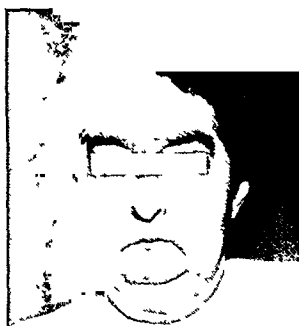


FIG. 1. Cushing's syndrome due to adrenal cortical cancer with metastasis. Patient had progressive weakness and obesity for 2 years, red, swollen face with hirsutism, acne, striae, diabetes and hypertension. Left kidney was displaced downward; metastases to the lungs and abdominal cavity were present. Urinary 17-ketosteroid excretion was 30 mg./24 hrs

left adrenal tumor with intra-abdominal and pulmonary metastasis at the time of examination (fig. 1). She died 5 months later. In the other patient, a 21 year old girl, Cushing's syndrome developed while she was under treatment for a metastatic adrenal cortical tumor; the patient died 13 months later.

In 4 patients the syndrome developed because of a solitary adenoma of the adrenal gland. One adenoma finally was found in a 40 year old woman (figs. 2 and 3), after three previous adrenal resections, located in an accessory adrenal underneath the pancreas. Two children, one 18 months old and the other 3 years,

<sup>3</sup> Sprague, R. G.: *Am. J. Med.*, 10: 567, 1951.

<sup>4</sup> Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, A. and Reifenshtein, E. C., Jr.: *J. Clin. Endocrinol.*, 1: 234, 1941.

<sup>5</sup> Corcoran, A. C.: Unpublished data.

<sup>6</sup> Forbes, A. P. and Albright, F.: *J. Clin. Endocrinol.*, 11: 926, 1951.

<sup>7</sup> McAlpine, H. T., Venning, E. H., Johnson, L., Schenker, V., Hoffman, M. M. and Browne, J. S. L.: *J. Clin. Endocrinol.*, 8: 591, 1948.

<sup>8</sup> Conn, J. W., Louis, L. H., Fajans, S. S., Johnson, B. J., Barott, G. W., Hogg, L. W., Blood, J. P. and Weiss, M. *Proc. Central Soc. Clin. Research*, 24: 23, 1951.

had large encapsulated adrenal cortical tumors which caused renal displacement. These were both considered adenomas although an unusual degree of cellular pleomorphism was present. All three of these patients are living, 5, 7, and 9 years later respectively. The fourth adenoma was found in a 53 year old woman who, unfortunately, died two months later of coronary infarction complicated by congestive heart failure.

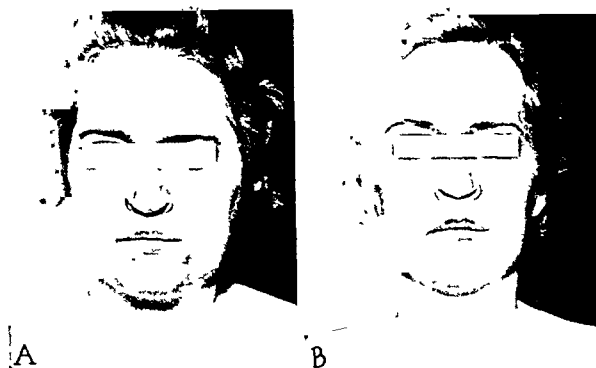


FIG. 2. *A*, Cushing's syndrome in 40 year old woman prior to therapy. *B*, subsequent to removal of accessory adrenal with adenoma.



FIG. 3. Accessory left adrenal with adenoma

Two additional patients with Cushing's syndrome had small adenomas occurring in otherwise hyperplastic adrenal glands. A man 25 years of age was found to have a large right adrenal gland containing a small adenoma. This gland was excised and two years later the patient appeared entirely normal. He received a total of 1600 roentgen units to the pituitary gland postoperatively, but in the light of present knowledge it is doubtful that this could have influenced pituitary function.<sup>9</sup> He is still alive 14 years after the operation. The other

<sup>9</sup> Hurxthal, L. M., Hare, H. F., Horrax, G. and Poppen, J. L.: *J Clin. Endocrinol.*, 9: 126, 1949.

patient was a 43 year old woman who had small adenomas in both adrenals. She died of adrenal failure following her second operation in 1947.

The remaining 20 patients were found to have normal sized or enlarged adrenal glands on exploration. It should be emphasized here that the size of a gland does not necessarily bear a direct relationship to its capacity of function or production of hormones. The range in weight of adrenal tissue removed in these 20 patients extended from 2.5 gm. to 27 gm. per gland. There may be variation in the weight of the two adrenal glands in the same patient. The average weight of the adrenal gland from a normal individual is considered to be between 2.5 to 7 gm. A few of the patients with Cushing's syndrome had intact glands removed which fell within this range of weight. The pathologist looks for certain features to make the diagnosis of adrenal cortical hyperplasia. These are rounded, nodular gland edges, increase of cellular elements, and increased fuchsinophilic staining reaction, considered by some pathologists to suggest cortical hyperfunction. A reliable method of testing cortical function of surgical specimens needs to be developed.

The key point in diagnosis is the recognition of the syndrome by the physician at the time of original examination, for if the diagnosis is not considered at this point it can be overlooked completely. Supplementing the clinical features enumerated previously are certain laboratory and roentgen findings usually encountered in patients with Cushing's syndrome. The glucose tolerance test is almost invariably compatible with diabetes mellitus, although the fasting blood sugar levels may be normal. Some of the patients have a rather severe insulin resistant type of diabetes. The peripheral blood characteristically shows lymphopenia with elevation of the hemoglobin and red blood cell count above normal levels. A few patients with severe Cushing's syndrome will show alteration of the serum electrolytes, with a low serum potassium, low chloride type of alkalosis, and elevation of the serum sodium. These changes are probably due to increased potassium excretion by the kidney with sodium and water retention. The electro-encephalogram will often reveal an abnormal pattern. Hypertension of variable degree is found, usually labile in nature, and often associated with cardiac enlargement and some degree of heart failure.

The measurement of the urinary 17-ketosteroids and corticoids is not always helpful, probably because these are only excretory products of metabolized adrenal steroids. With adenomas or adrenal cortical hyperplasia, the 17-ketosteroid excretion may be normal or slightly elevated but with malignant cortical tumors the amount excreted may become large.<sup>6</sup> The urinary corticoid levels by present chemical tests are not usually diagnostic in Cushing's syndrome.<sup>5</sup>

Osteoporosis is common among patients with Cushing's syndrome, involving chiefly the skull, ribs and vertebrae. Pathologic fractures of the ribs and spine are common. Skull roentgenograms almost invariably show a normal sella turcica but if widening of the sella is present it may be assumed that there is a pituitary tumor. Such occurrences are rare. The excretory urogram is the most useful roentgenographic examination of the adrenal glands; downward displacement or outward rotation of the upper pole of a kidney may indicate the

presence of an adrenal tumor. Additional help may be provided by retrograde pyelograms, perirenal gas insufflation as practiced in some clinics, and spot films focused at the level of the adrenals to bring out soft tissue detail. Translumbar aortography will show the blood supply of a large adrenal tumor but it has not proved helpful to us in demonstrating small tumors or adrenal hyperplasia.

Preoperative localization of an adrenal tumor greatly simplifies the surgical handling of a patient with Cushing's syndrome for the tumor can be removed via the flank or thoracolumbar approach without the need of exploring both adrenals. Usually no tumor is located by preoperative roentgen studies and, therefore, simultaneous bilateral adrenal exploration should be performed. It is important to inspect both adrenal glands before any definitive procedure is done. Small benign adrenal tumors usually cause atrophy of the opposite gland. Such

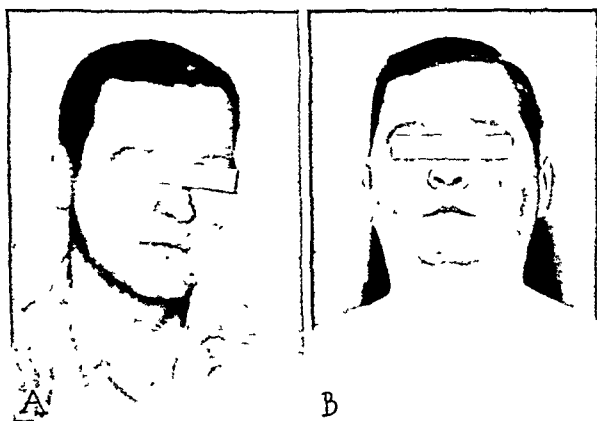


FIG. 4. Cushing's syndrome due to bilateral adrenal hyperplasia. A, one year prior to onset of illness. B, patient's main complaint was back pain, due to osteoporosis, and generalized weakness.

tumors should be enucleated or the entire gland excised if there is doubt as to its nature. If both adrenals appear atrophic a search must be made for a cortical adenoma in an aberrant location. Accessory adrenal tissue may be present in one out of five people.

Adrenal exploration on three out of four occasions in patients with Cushing's syndrome will reveal hyperplastic glands (figs. 4 and 5), often difficult to distinguish from normal structures. According to the present concept of therapy, one entire gland and most of the opposite adrenal should be excised,<sup>10, 11</sup> sparing only a fragment containing the arterial supply and the central adrenal vein. Bilateral subtotal adrenalectomy can be done readily in one operation, preferably under constant spinal anesthesia, utilizing Young's approach of posterolateral incisions<sup>12</sup> and excision of the twelfth rib. There is little risk involved in this

<sup>10</sup> Priestley, J. T., Sprague, R. G., Walters, W. and Salassa, R. M.: *Ann. Surg.*, **134**: 464, 1951.

<sup>11</sup> Poutasse, E. F. and McCullagh, E. P. *J. Urol.* **63**: 779, 1952

<sup>12</sup> Young, H. H.: *Surg. Gynec. & Obst.*, **63**: 179, 1936.

operation now that adequate replacement therapy is available; eight patients with Cushing's syndrome have been treated by this method in the last year without fatality.

What was formerly the most difficult part of the surgical management of Cushing's syndrome is now relatively simple and reliable since steroid hormones are available. All patients should be given protective cortisone prior to adrenal surgery. Operative stability is provided by administering 100 mg. of cortisone intramuscularly about 12 hours ahead, repeated again a few hours before operation. This should be continued after operation in doses of about 50 mg. every 6, 8 or 12 hours, depending on the necessity. Gradually withdraw the dosage as the patient recovers, and within three to six weeks there should be no further need. Signs and symptoms of adrenal insufficiency must be carefully watched for. These are nausea and vomiting, weakness, muscle pains or stiffness, hypo-

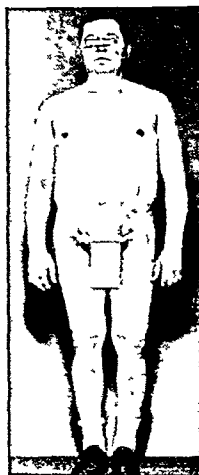


FIG. 5. Full length view

tension, or unexplained fever. If these develop, treatment with cortisone must be instituted promptly before acute adrenal failure ensues. In some instances cortisone may have to be given continuously because of failure of the adrenal fragment remaining in the body to furnish sufficient hormones to maintain health. Adrenocorticotrophic hormone (ACTH) can be utilized to stimulate an atrophic adrenal.

There is usually sufficient desoxycorticosterone-like action in cortisone to supply the daily need of this hormone in most patients. It may be necessary to use desoxycorticosterone (DOCA) in doses of 1 to 3 mg. daily in some patients who have low serum sodium values not sustained by added salt in doses of  $\frac{1}{2}$  to 6 gm. daily as enteric coated salt tablets.

Blood electrolyte values must be carefully followed after operation, for serious alteration of serum sodium, potassium, chloride and carbon dioxide combining power can occur, necessitating the use of intravenous saline or potassium and

desoxycorticosterone. Blood sugar levels must also be checked frequently, for a patient with Cushing's syndrome can switch from an insulin resistant diabetes to severe insulin sensitivity immediately following subtotal adrenalectomy. If a shock-like state develops postoperatively and the patient has received adequate cortisone, hypoglycemia may be the cause, in which case hypertonic glucose will revive the patient.

It is difficult to estimate how much adrenal tissue to leave in the body but experience has shown that about 90 per cent must be removed. At present it is not considered justifiable or necessary to remove all of both adrenal glands unless the disease is progressive following subtotal adrenalectomy, and a serious threat to life. Total adrenalectomy has been done in a few instances on an experimental basis for Cushing's syndrome.<sup>13</sup>



Fig. 6. A, twenty-four year old man with Cushing's syndrome due to bilateral adrenal hyperplasia. B, patient 7 years subsequent to bilateral hemi-adrenalectomy.

The results are encouraging in the 8 patients with Cushing's syndrome due to adrenal cortical hyperplasia treated in the last year and a half since cortisone came into use, but as yet incomplete. One required secondary total adrenalectomy for control of the disease. One patient died 9 months after operation because of shock from an uncontrolled duodenal ulcer hemorrhage. He was better in all respects except for his hypertension, which may have contributed to his death. The remaining patients are all improved or have too short a follow-up period to be of value. One woman requires daily cortisone to keep her from experiencing adrenal failure but she had a virtually complete remission of her disease.

Twelve patients with Cushing's syndrome due to adrenal hyperplasia were treated during the period 1933 to 1950. A 17 year old girl underwent what was known as adrenal denervation by Dr. George Crile, Sr. in 1933. She had a complete recovery from her disease but died two years later of measles and acute adrenal failure. At autopsy both adrenals appeared atrophic. Five patients

<sup>13</sup> Personal communications to the authors

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FIG. 5. Full length view

tension, or unexplained fever. If these develop, treatment with cortisone must be instituted promptly before acute adrenal failure ensues. In some instances cortisone may have to be given continuously because of failure of the adrenal fragment remaining in the body to furnish sufficient hormones to maintain health. Adrenocorticotrophic hormone (ACTH) can be utilized to stimulate an atrophic adrenal.

There is usually sufficient desoxycorticosterone-like action in cortisone to supply the daily need of this hormone in most patients. It may be necessary to use desoxycorticosterone (DOCA) in doses of 1 to 3 mg. daily in some patients who have low serum sodium values not sustained by added salt in doses of 4 to 6 gm. daily as enteric coated salt tablets.

Blood electrolyte values must be carefully followed after operation, for serious alteration of serum sodium, potassium, chloride and carbon dioxide combining power can occur, necessitating the use of intravenous saline or potassium and

desoxycorticosterone. Blood sugar levels must also be checked frequently, for a patient with Cushing's syndrome can switch from an insulin resistant diabetes to severe insulin sensitivity immediately following subtotal adrenalectomy. If a shock-like state develops postoperatively and the patient has received adequate cortisone, hypoglycemia may be the cause, in which case hypertonic glucose will revive the patient.

It is difficult to estimate how much adrenal tissue to leave in the body but experience has shown that about 90 per cent must be removed. At present it is not considered justifiable or necessary to remove all of both adrenal glands unless the disease is progressive following subtotal adrenalectomy, and a serious threat to life. Total adrenalectomy has been done in a few instances on an experimental basis for Cushing's syndrome.<sup>13</sup>

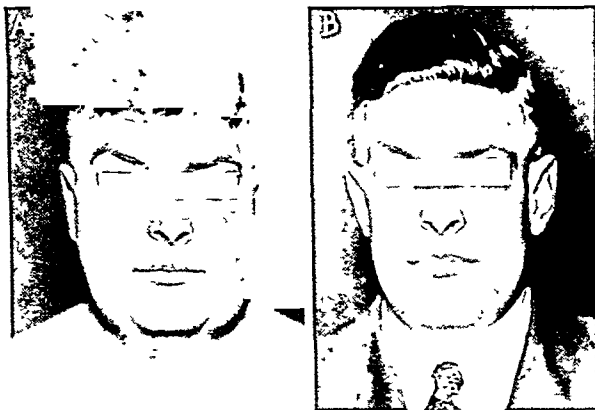


FIG. 6. A, twenty-four year old man with Cushing's syndrome due to bilateral adrenal hyperplasia. B, patient 7 years subsequent to bilateral hemi-adrenalectomy.

The results are encouraging in the 8 patients with Cushing's syndrome due to adrenal cortical hyperplasia treated in the last year and a half since cortisone came into use, but as yet incomplete. One required secondary total adrenalectomy for control of the disease. One patient died 9 months after operation because of shock from an uncontrolled duodenal ulcer hemorrhage. He was better in all respects except for his hypertension, which may have contributed to his death. The remaining patients are all improved or have too short a follow-up period to be of value. One woman requires daily cortisone to keep her from experiencing adrenal failure but she had a virtually complete remission of her disease.

Twelve patients with Cushing's syndrome due to adrenal hyperplasia were treated during the period 1933 to 1950. A 17 year old girl underwent what was known as adrenal denervation by Dr. George Crile, Sr. in 1933. She had a complete recovery from her disease but died two years later of measles and acute adrenal failure. At autopsy both adrenals appeared atrophic. Five patients

<sup>13</sup> Personal communications to the authors.



underwent bilateral hemi-adrenalectomy; three now appear entirely normal, a fourth is improved, but the fifth died of postoperative adrenal failure. Five additional patients underwent operative investigation only of the adrenal glands. Three of these died of complications of Cushing's syndrome; two we have been unable to follow. One man with Cushing's syndrome, treated solely with testosterone, showed only slight improvement and died six years later of cancer of the esophagus.

With adequate resection of adrenal tissue most, if not all, abnormal features of the syndrome improve: the skin becomes normal in color and texture, hirsutism disappears, muscles strengthen and obesity vanishes; menstruation returns in women, glucose tolerance test returns to normal and those with diabetes show improvement. Osteoporosis does not show the same rate or degree of improvement and it may take several years for the bones to appear normal. Hypertension does not always improve following subtotal adrenalectomy, possibly because of extensive vascular disease already present.

A few points regarding the late results of treatment of Cushing's syndrome are of interest. A 27 year old woman who was amenorrheic prior to her operation in 1947, has since given birth to two normal children. One man who underwent adrenal surgery in 1938 at the age of 25 and became normal, recently returned to the Cleveland Clinic with coronary infarction. Another man, similarly treated in 1943 at the age of 24 (fig. 6), with a satisfactory remission, sustained a coronary infarction one year ago. He also has intermittent claudication of both legs and occlusion of his right external iliac artery. These two men suggest that serious vascular disease may occur at an early age in patients with Cushing's syndrome in spite of adequate therapy.

#### SUMMARY

All patients with Cushing's syndrome are believed to have hyperadrenocorticism with excess production of 11-oxysteroids. In three out of 4 instances it is due to adrenal hyperfunction with or without hyperplasia of the gland, the remaining patients have either a benign or malignant cortical tumor. Rarely, the initiating cause of the syndrome is a basophilic pituitary tumor. The syndrome can be produced by ACTH, cortisone, or compound F.

The diagnosis of Cushing's syndrome depends on clinical observation supported by key laboratory evidence. Roentgenographic studies are helpful in locating a sizeable adrenal tumor but not a small one.

Treatment consists of excision of a tumor if present, or subtotal adrenalectomy. The operation can be done on both adrenals simultaneously without undue risk. The use of cortisone and other hormones for replacement therapy is discussed. Results of treatment of twenty-eight patients with Cushing's syndrome are presented. At present it is not considered necessary to perform bilateral total adrenalectomy unless the disease is progressive following subtotal adrenalectomy and a threat to life.

## PRE- AND POSTOPERATIVE CARE IN ADRENAL SURGERY

JOSEPH W. JAILER

*From the Departments of Obstetrics and Gynecology and of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.*

Specific problems of adrenal surgery have been discussed by the previous speakers. I should like to review the overall topic and discuss problems and therapy in the light of our knowledge of adrenal physiology and steroid chemistry.

Bilateral total adrenalectomy without suitable replacement therapy in the experimental animal invariably results in death within 10 days. Addison's disease was considered a fatal condition. With the synthesis and widespread use of desoxycorticosterone (DCA) in this condition, this was no longer considered so. However, it soon became evident in clinical practice as well as in the study of the experimental animal deprived of its adrenals, that this steroid (DCA) alone could not be used for complete adrenocortical replacement. DCA in itself does not have all the physiological effects necessary to cope with crises which may develop. Adrenal cortical extract had to be used to supplement the former steroid. Therefore it is only since the introduction of cortisone into the armamentarium of the clinician that it has been possible to perform radical adrenal surgery with little risk. Total adrenalectomy was performed in the pre-cortisone era; however, results were not satisfactory since life could not be maintained for sufficient length of time due to the relative impotency of the adrenocortical extracts available.

Before discussing replacement therapy I should like to review briefly some of the aspects of adrenal physiology and chemistry (table 1). As you know, several different biologically active steroids have been isolated from adrenal tissue of animals. The adrenal cortex, as an endocrine gland, differs from the thyroid, pancreas and testes in that some of the steroids elaborated in the adrenal have markedly different physiological effects. It is with an understanding of these principles that we can better prepare a patient for adrenal surgery and maintain normal homeostasis postoperatively.

Desoxycorticosterone, as the name implies (Desoxy), lacks an oxygen at the eleventh carbon; its effect is primarily on salt and water metabolism, having but little effect on protein and carbohydrate metabolism. Moreover there is a paradox in its action in that DCA can maintain the life of the adrenalectomized animal but is not very effective in protecting the animal against a stress—cold, infection, toxins, etc. The 11-oxysteroids on the other hand as represented by cortisone, compound F and to a lesser extent corticosterone or compound B are more effective against stress. They effect protein catabolism, gluconeogenesis, cause a fall in eosinophils and lymphocytes and increase the capacity of muscles to perform work. They are salt-retaining steroids as well but are not as efficient as desoxycorticosterone. One of their important effects is to suppress ACTH production by the pituitary.

Another hormone at our disposal is ACTH; suffice it to say that for all prac-

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J.

tical purposes its effects are mediated through the adrenal and it is ineffective in the absence of the adrenal cortex.

We do not know, at present, which steroids the human adrenal secretes. There is some evidence that compound F may be one of them however. There is no direct proof that DCA itself is secreted.

Adrenal surgery is performed for several different reasons and in different diseases. In order to understand the therapy employed, certain concepts of the disease must be borne in mind.

1) Total adrenalectomy has been performed for malignant hypertension, prostatic and mammary carcinoma. We have had very little personal experience in this field and I am embarrassed to discuss this in front of Doctors Baker and Harrison since the regimen outlined is taken from their published works. If adrenalectomy is done in two stages, usually no special preparation is necessary for the first stage. The following regimen is usually followed for the second stage or when a bilateral operation is performed at one sitting. Day before operation: The patient is given 200 mg. cortisone intramuscularly, since this will have its greatest effect the following day. On the day of the operation 200 mg. more

TABLE 1. *Comparison of the active corticosteroids by different assay methods*

| COMPOUND | SURVIVAL TEST | Na RETENTION | INGLE TEST | ANTI-INSULIN | GLYCOGEN DEPOSITION |
|----------|---------------|--------------|------------|--------------|---------------------|
| "B"      | 1+            | 2+           | 2+         | 2+           | 3+                  |
| "F"      | 1+            | 0            | 4+         | 4+           | 4+                  |
| "E"      | 1+            | 0            | 4+         | 4+           | 4+                  |
| DCA      | 4+            | 4+           | 0          | 0            | 0                   |

plus 5 mg. DCA. First day postoperative—200 mg. plus 5 mg. DCA → cortisone is then tapered off gradually.

2) Adrenalectomy for Cushing's syndrome: It has not been definitely established whether Cushing's syndrome is primarily pituitary or primarily adrenal cortical disease. (In other words, too much ACTH versus too much compound F). However, there is no doubt that the clinical manifestations of the disease are due to excessive corticoid secretion. All the signs and symptoms of the disease have been produced by chronic administration of large doses of cortisone. Therefore, removal of the source of these steroids is a rational approach to therapy in this condition.

Cushing's syndrome may be due to an adrenocortical adenoma or carcinoma. When this pathological condition occurs there can be no dispute as to the course of action. It should be borne in mind however that when a tumor exists in the presence of this clinical entity, the contralateral adrenal gland is invariably atrophic; so that if no hormonal preparation is done prior to the removal of the tumor, the surgeon may find himself with an essentially adrenalectomized patient who has just been severely stressed. Such a condition is not compatible with life. The rationale of therapy is replacement with cortisone and DCA for the immediate replacement effect together with ACTH to stimulate the function of that atrophic contralateral gland (table 2).

If in the immediate postoperative period, the blood pressure falls, infusions of nor-adrenaline or neo-syneprine and blood should be employed.

Serum sodium and potassium levels should be carefully followed and these electrolytes replaced, of course, if their concentrations fall. This is especially so for the K which may be lost in the urine as a result of excessive cortisone replacement therapy.

TABLE 2. *C. R., Cushing's syndrome*

| DATE         | Na.     | K.          | Cl.   | CO <sub>2</sub> | TREATMENT                                |
|--------------|---------|-------------|-------|-----------------|------------------------------------------|
|              |         | (mEq/liter) |       |                 |                                          |
| 12/10        | 143.0   | 2.3         | 92.2  | 39.6            |                                          |
| 12/11        | 144.0   | 2.6         | 93.0  | 41.8            | 200 mg. "E"                              |
| 12/12        | Surgery |             |       |                 | 300 mg. "E"; 5 mg. DCA; 25 mg. ACTH i.v. |
| 12/13 (a.m.) | 144.1   | 2.1         | 94.3  |                 | 200 mg. "E"; 5 mg. DCA; 25 mg. ACTH i.v. |
| 12/14 (a.m.) | 139.0   | 2.1         | 92.2  | 35.1            | 200 mg. "E"; ACTH i.v.                   |
| 12/15        | 141.0   | 2.6         | 96.9  | 35.0            | 100 mg. "E"; ACTH i.v.                   |
| 12/16        |         |             |       |                 | 75 mg. "E"; ACTH i.v.                    |
| 12/17        | 141.7   | 2.5         | 96.5  | 38.7            | 50 mg. "E"; ACTH i.v.                    |
| 12/18        | 140.3   | 1.9         | 93.5  | 36.6            | 25 mg. "E"; ACTH i.v.                    |
| 12/19        | 142.3   | 2.2         |       |                 | 25 mg. "E"; 15 mg. ACTH i.v.             |
| 12/20        | 140.6   | 2.4         |       |                 | 25 mg. "E"; 10 mg. ACTH i.v.             |
| 12/22        | 140.5   | 2.8         | 99.6  | 34.3            |                                          |
| 12/26        | 141.5   | 3.5         | 100.0 | 30.2            |                                          |

TABLE 3. *Steroidal pre- and postoperative care for adrenalectomy in Cushing's syndrome*

## Preoperative

Day 2 200 mg. cortisone i.m.

Day 1 200 mg. cortisone i.m.

Day of adrenalectomy—100 mg. cortisone early a.m.—5 mg. DCA

## Postoperative

Day 1 200 mg. cortisone 5 mg. DCA

Day 2 200 mg. cortisone 5 mg. DCA

Day 3 200 mg. cortisone DCA if needed

Day 4 150 mg. cortisone DCA if needed

Day 5 Gradual tapering of cortisone dosage

Cushing's syndrome is more frequently due to adrenal hyperplasia than neoplasm. Even though in some cases the adrenals may not be enlarged anatomically, there is no doubt of their physiologic over-activity. Occasionally a spontaneous remission may occur. Furthermore, in the series at the Presbyterian Hospital about one-third of the patients have benefited by radiation of the pituitary gland. But apparently it becomes necessary to operate on a good number of these patients. Between 90–100 per cent of the adrenal tissue must be removed in most cases to effect a remission in this condition, otherwise regeneration of the remaining tissue may again result in the disease.

The usual routine is to remove 90 per cent of one adrenal and at some future date to do a complete adrenalectomy on the contralateral side. If one side is to

be removed, aside from the usual surgical precautions, no hormonal support is necessary. It must be borne in mind that these patients heal poorly and wounds disrupt easily. We have recently followed three hyperadrenal patients through an uneventful single stage adrenalectomy without any steroidal support.

It is with the second stage that we are concerned. As a result of the surgical procedure the patients proceed from a state of hyperadrenalism to one of hypoadrenalism with all the attendant metabolic effects. Therefore, the transformation must be made gradual. Preparation in these cases proceeds as it does in the total adrenalectomy. For two days preoperatively we have given 200 mg. intramuscular cortisone which is continued for several days thereafter, the length of time depending upon the clinical condition as well as the electrolyte and carbohydrate state. Following this, the dose of cortisone is gradually tapered down. Anywhere from 12.5 to 50 mg. a day is needed to maintain the patients. Some may require none at all. DCA is given on the day of operation and the first postoperative day. This is continued only if needed as judged by the concentration of sodium in the serum. This is summarized in table 3.

3) Adrenogenital syndrome: The adrenogenital syndrome or adrenal virilism also concerns the genito-urinary surgeon. Here, too, the cause may be adrenal hyperplasia or neoplasm. Due to the differences in the steroids elaborated by the adrenal in this condition as compared to the Cushing's syndrome the metabolic alterations are not at all similar and the operative procedure is attendant with different problems. The metabolic alterations in CHO, protein and electrolyte spheres are not present. These patients withstand surgery well, heal promptly and are no problem. In our experience, very little or no hormonal support is needed. One word of caution is necessary, and this must be stressed, adrenal carcinoma showing the mixed syndrome, namely elements of both the adrenogenital syndrome and Cushing's, should be handled like the latter. They differ from the true Cushing in that in addition to excessive corticoid secretion the adrenals are elaborating androgens as well. They must be prepared for operation with hormonal support as outlined above. The patients with benign adenomas, on the other hand, require no hormonal support.

Being an internist, I should like to close this discussion with a demonstration of how a medical adrenalectomy can be performed. As you know, ACTH stimulates the adrenal cortex and, conversely, cortisone or compound F inhibits the pituitary from secreting more ACTH. Thus, in patients with adrenal virilism due to bilateral adrenal hyperplasia, the administration of cortisone results in an indirect decrease of adrenal secretion and at the same time the substitution of a more normal adrenal steroid for the abnormal ones being elaborated in this syndrome.

When a carcinoma is present, on the other hand, cortisone is without effect upon the 17-ketosteroids. We have one further piece of evidence to uphold the thesis that adrenal carcinoma is completely independent of pituitary stimulation. One of our patients with an adrenal carcinoma and Cushing's syndrome was subsequently hypophysectomized. This procedure had no effect on the course of the disease nor on the 17-ketosteroids.

## WILMS'S TUMOR IN AN ADULT: REPORT OF A TEN YEAR CURE

GEO. R. LIVERMORE

Wilms's tumor in the adult is rare and, as far as can be determined, the prognosis is even worse than in children. For these reasons, it was believed that the following case report of a more than 10 year survival would be of interest.

### CASE REPORT

Mrs. C. F., a 37 year old white woman, first consulted us on June 16, 1941. She gave a history of having noticed a firm, round, nontender mass in her right loin shortly after the delivery of her only child in 1938. A diagnosis of floating kidney was made elsewhere and the patient wore a kidney support until December 1940, when she had an attack of right renal colic. An excretory urogram showed a kinked right ureter which was believed to be the cause of her colic. She had no further attacks, but the mass gradually increased in size, and there was a sense of weight and dull aching pain in her right loin. The urine was never grossly bloody but a few red blood cells were present at that time. In January 1941, the patient began to have fever without chills and her pain increased. The mass became markedly tender, and on January 15, 1941 her local physician performed an exploratory operation at which time a perirenal abscess and a tumor mass were found. A biopsy was obtained of the mass and the abscess drained. The biopsy revealed Wilms's tumor. Past and family histories were non-contributory.

The physical examination was within normal limits except for the right lumbar region. The surgical incision was still draining mucopurulent material 5 months after the exploration. A firm, round mass the size of a medium grapefruit was felt below the right costal margin. It seemed continuous with the right kidney. It was firmly fixed and nontender. Routine laboratory studies were normal.

Cystoscopy revealed chronic cystitis with normal ureteral orifices. No. 5 catheters were easily passed to both pelvises with a moderate flow of clear urine from the left and none from the right. Indigo carmine appeared in 2½ minutes and was deep in 4 minutes from the left. No dye appeared from the right in 30 minutes. The x-ray of the kidneys, ureters and bladder showed no stones and a large mass continuous with the lower pole of the right kidney extending 1 inch below the crest of the ilium. The right pyelogram showed some dilatation of the pelvis and calyces (fig. 1). The lower calyx was shortened and the entire pelvis pushed upward. The ureter was pushed over to the midline of the vertebral bodies. The left pyelogram was normal. Urine from the left kidney showed 7 white blood cells and a few red blood cells per high powered field and staphylococci grew on culture.

Deep x-ray treatments were administered by Dr. Shields Abernathy from June 17 to July 2, 1941. The patient received a total of 4100 r. through a 10 cm. cone over two portals, one anterior and one posterior, the factors being 200 Kv., 25 Ma., filter 5 mm. Cu., T. S. D. 60 cm. Treatments were begun at 250 r. per

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 19, 1952.

day for two days and then increased to 300 r. per day for the rest of the course. There were no unfavorable side reactions.



FIG. 1. Retrograde pyelogram. Note dilated pelvis.



FIG. 2. *A*, Low power (X100) photomicrograph of one section through tumor. *B*, high power (X430) photomicrograph of same section.

The patient was seen again on August 15, 1941, six weeks after the last x-ray treatment. The tumor had decreased 25 per cent in size and was movable. The red cell count was 4,100,000 and the hemoglobin 88 per cent. A 500 cc transfusion was given prior to surgery.

On August 17, 1941 a right nephrectomy was performed. Because of the size and fixation of the tumor when first seen, we had planned a transperitoneal approach. The response to x-ray, however, had been so satisfactory that the usual lumbar extraperitoneal approach was used without difficulty. The upper two-thirds of the kidney appeared normal but somewhat distorted. The tumor mass involved the lower pole and was the size of a medium grapefruit. It was adherent to the vena cava for a distance of three inches but was easily freed and removed (although I held my breath while stripping it off the vein). The postoperative recovery was uneventful and the patient left the hospital on the tenth day. The wound was completely healed in three weeks.

The pathological report by Dr. N. E. Leake was Wilms's embryonal tumor. This diagnosis was confirmed by the Carcinoma Registry of the A.U.A.

The patient was last seen on April 15, 1942. She had gained 15 pounds and felt in perfect health. There was no evidence of recurrence. A letter from her, dated January 30, 1952, states that she is "still well and doing fine." She continues to have periodic check-ups 11 years after the biopsy by her local physician and 10½ years after nephrectomy.

#### DISCUSSION

The rarity of Wilms's tumor in the adult has led to numerous reports of individual cases and considerable discrepancy as to the total number of such cases.

The two most complete recent reviews are those of Esersky, Saffer, Panoff and Jacobi<sup>1</sup> and of Culp and Hartman.<sup>2</sup> The former collected 53 cases, added three of their own and mention still another case, the fifty-seventh, reported while their paper was in preparation. These authors include a table listing the age and source of their 56 cases.

Culp and Hartman, in an even more extensive review, collected 97 cases from the literature and reported six of their own. They emphasize the difficulties and inaccuracies of such a review: Some cases had been wrongly included in previous reviews due to misinterpretation; other cases, masquerading under different titles, had been overlooked. They found over 50 different names applied in the literature to embryonal renal tumors. They suggest the name "embryonal nephroma" for the entire group, which they then subdivide into tumors of cortical origin, "mesoblastic nephromas," and those of pelvic origin, "mesonephric nephromas." They further subdivided the mesoblastic group into carcinoma, sarcoma, mixed, and undifferentiated types. On the basis of their studies of the histology and the very similiar clinical behavior of these subgroups, they believe that they have a common pathogenesis and probably all arise as the mixed type, with subsequent preponderance of one or the other cell type. They also believe that most, if not all, sarcomas arising in the renal cortex are embryonal tumors.

Culp and Hartman collected at least 143 mesoblastic nephromas. There were several "possible" cases and one whole review of 35 cases had to be omitted as

<sup>1</sup> Esersky, G. L., Saffer, S. H., Panoff, C. E. and Jacobi, M.: *J. Urol.*, 58: 397, 1947.

<sup>2</sup> Culp, O. S. and Hartman, F. W.: *J. Urol.*, 60: 552-76, 1948.



its authors made no distinction between cortical and capsular sarcomas although both types had been included. The mixed cell type, including classical Wilms's tumors, was the most common morphological variant with 97 cases from the literature plus 6 added by the authors. They fail to present an actual list of the 97 cases, but their very complete bibliography is subdivided according to cell type. Even so, it is impossible to count 97 cases despite the fact that some authors reported up to 4 cases.

To add further to the bibliographic confusion, Culp and Hartman do not include the 3 cases of Esersky, Saffer, Panoff, and Jacobi, nor do they include in the bibliography 7 other cases cited by that group (Lubarsch [4 cases], Maas, J. J. Moore, and Nicholson). Since Culp and Hartman list the cases they purposely excluded from their series, it seems likely that these 7 cases were overlooked by them, a possibility they freely admitted in their introductory remarks. Therefore, it is impossible to state just how many cases of Wilms's tumor in the adult have been reported without further exhaustive study of the literature. Should this be attempted again in the future, we believe that a nearly accurate report can be made by integrating the bibliographies of these two papers.

The overall prognosis of Wilms's tumor is notably poor, and the general impression is that it is even worse in the adult. Culp and Hartman<sup>2</sup> in 1948 were able to collect only 8 survivals of 3 or more years from 97 adult cases. At the time of their inquiry (1947), 4 patients had lived 15, 11, 8, and 6 years at a time when the patient reported here had survived but 5 years.

X-ray has long been used with good result in the treatment of Wilms's tumor. No 5-year cures have followed its use alone, but combined with surgery it seems to improve the prognosis and often to make otherwise inoperable lesions operable. Ladd<sup>3</sup> believes that transperitoneal nephrectomy can be safely performed in almost all cases of Wilms's tumors without preoperative radiation which wastes valuable time during which further extension of the tumor may occur. His opinion must be respected because of the superiority of his results over those of other comparable series; however, it has been suggested<sup>4</sup> that the average surgeon confronted with the usual Wilms's tumor occupying one-half or more of the abdomen might not perform a primary nephrectomy with the facility of Dr. Ladd and might obtain better results after preoperative x-ray. Indeed, this seems the treatment of choice with most authors if the diagnosis can be made. The poorer prognosis in the adult has been attributed to the failure of diagnosis and consequent failure to make use of preoperative radiation. We are certainly of the opinion that preoperative x-ray was of great benefit in our case.

The preliminary biopsy was also a decided help to us, for without it, x-ray therapy might not have been used. One would certainly not, however, go so far as to recommend such a procedure because the possibility of further dissemination of so malignant a tumor by the biopsy far outweighs its advantage. The patient would also be subjected to two operations in complete disregard of Ladd's opinion that the prompt total removal of the tumor is the best treatment anyway.

<sup>3</sup> Ladd, W. E. and White, R. H.: *J. A. M. A.*, **117**: 1858-1863, 1941.

<sup>4</sup> Weisel, W., Dockerty, M. B. and Priestley, J. T.: *J. Urol.*, **50**: 399-413, 1943.

Indeed, there are several factors about the present case which would lead one to anticipate something quite different from the happy outcome which obtained. Over 3 years elapsed between appearance of the mass and nephrectomy. The tumor was incised for biopsy 5 months before definitive treatment. Finally, the operative wound still presented a draining sinus when the patient was first seen. It is interesting to speculate whether the inflammatory reaction accompanying the perirenal abscess might not have been a factor in keeping the tumor localized in the face of the other more apparent factors favoring its dissemination.

#### SUMMARY

A case of Wilms's tumor in the adult has been presented. Symptoms (mass) were present 3 years before nephrectomy, and a biopsy was performed 5 months before definite treatment was instituted. Preoperative x-ray therapy was utilized followed by extraperitoneal nephrectomy. The patient is alive and well over 10 years after surgery. Long survivals in 4 cases of Wilms's tumor in the adult were found in the literature. Two cases had already survived 11 and 15 years in 1947. Two other cases had lived 6 and 8 years respectively at that time, and if still alive represent longer survivals than the present case.

*Hickman Arts Bldg., Memphis 3, Tenn.*

## SILENT ADENOCARCINOMA OF THE KIDNEY WITH SOLITARY METASTASES OCCURRING IN BROTHERS

CARL RUSCHE

Barney and Churchill in 1939, and Hager in 1941, reported before this society an instance of silent adenocarcinoma of the kidney (hypernephroma) with solitary metastasis in whom a successful removal of both parent and metastatic lesion was accomplished.

The vagary of metastasis of hypernephroma is well-recognized and while distant metastases may occur in almost any bodily structure, the thorax and cranial contents appear most vulnerable. The singular capacity of giving rise to a solitary metastasis, and the development of a metastasis many years after the removal of the primary tumor, are features of unusual distinction. Since they have the same genesis both the primary and secondary lesion are slow and indolent in their growth. Recent literature attests to unusual interest, and to the evolution of certain criteria which would extend the application of surgical procedures to those individuals who in the past have been deprived of more radical treatment. This is of particular import in the field of brain surgery. It has been estimated that approximately 10 per cent of all hypernephromas metastasize to the brain and in the majority, the lesion appears single.

Störtebecker of Sweden reported a group of 19 cases with metastasis to the brain from hypernephroma of whom 17 were operated. The surgical mortality was 30 per cent. One patient lived 14 years following the brain surgery. The most favorable prognosis appears to be in those cases in which a nephrectomy was done prior to the development of symptoms denoting cerebral involvement. Obviously, where general metastases are evident, nothing is gained by operating on a cerebral metastatic tumor.

An instance of silent adenocarcinoma of the kidney, occurring in brothers in whom the cardinal symptoms emanated from the metastatic lesion, is recorded.

### CASE REPORT

*Case 1.* R. D., a physician, 33 years of age, consulted us September 7, 1940, complaining of an insidious onset of fatigue, malaise, perspiration, slight weight loss, and pain in the right scapular region and in the left thigh. The duration of the symptoms was 3 months, during which time he had been examined by an internist and an orthopedist. They were unable to arrive at a diagnosis.

The patient's mother died at 52 years of age of coronary thrombosis; his father, 6 brothers and 3 sisters were living and well. The past history concerning his paternal and maternal grandparents was not available. The past history was irrelevant except that the patient specialized in diseases of the chest and the clinical symptoms were closely allied to those of tuberculosis.

Physical examination revealed a well-developed and nourished man who was perspiring profusely. The temperature was 99.8 degrees, and blood pressure 115 diastolic and 75 systolic. The pain in the right shoulder was especially marked

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 19, 1952.

upon external rotation of the arm. Slight bilateral enlargement of the inguinal glands was present. The abdomen revealed no rigidity or tender points. The left kidney was palpable. The prostate was entirely normal. Urinalysis was chemically and microscopically negative. The blood demonstrated 4,250,000 erythrocytes, lymphocytes 5,700, and hemoglobin 75 per cent.

Roentgenographic examinations of the pelvis, lumbar spine, hips, femurs and skull were normal. However, the chest films, which showed normal lung fields, demonstrated an area of diminished bone density in the tenth rib on the right side near the posterior axillary line. A biopsy taken from the area showed the tumor tissue invading the bone marrow of the rib and occupying spaces between the bone spicules. The tumor was composed of large polyhedral cells having an abundant granular to foamy cytoplasm and large hyperchromatic vesicular nuclei in which one or more nuclei were large and prominent.

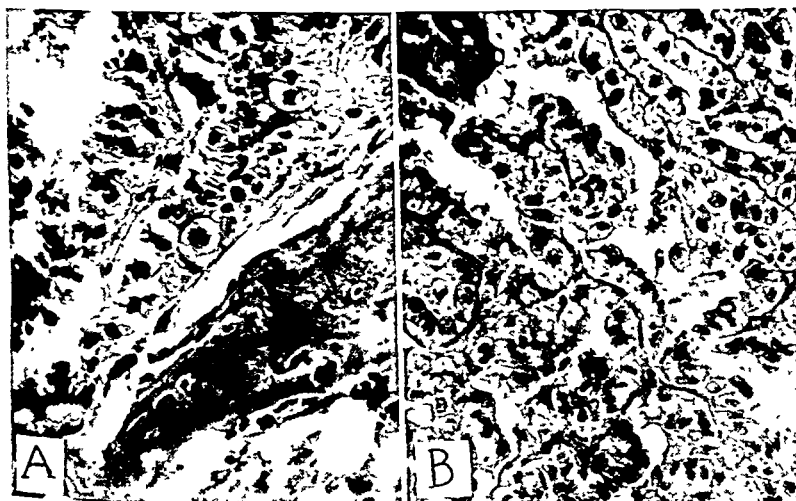


FIG. 1. A, representative section of lesion from tenth rib on right side. Masses of tumor cells are invading marrow between bone spicules. B, photomicrograph of renal tumor, showing papillary arrangement of polygonal and cuboidal cells with granular cytoplasm, with marked variation in size and shape of nuclei.

The tumor cells were arranged in an indefinite papillary arrangement in contradistinction to an alveolar formation, although most of the tumor cells were in large masses between the bone spicules. Mitotic figures were occasionally seen. Considerable hemorrhage was present in the tumor, with reactionary osteitis fibrosa at the margin of the lesion. The histological diagnosis: metastases to the rib from a granular cell papillary type of adenocarcinoma of the kidney (fig. 1, A).

In view of the biopsy examination, although there were no symptoms or findings of a renal lesion, a cystoscopy and retrograde pyelograms were carried out. The bladder was normal; clear jets of urine appeared from each ureteral orifice. Catheters were introduced without obstruction. The function was satisfactory and urine specimens were negative. The right kidney and ureter were normal. The left renal shadow was enlarged, irregular, suggesting lobulation. The calyces were clubbed and dilated. The lower minor calyx was elongated with a sickle-shaped deformity consistent with a tumor of the kidney.

Removal of the solitary metastasis in the rib and left nephrectomy were advised. The patient refused surgery. The clinical course was rapidly downward, with death occurring 5 months after the diagnosis was confirmed, making a total of 8 months subsequent to the onset of the bizarre symptoms.

The necropsy revealed an adenocarcinoma of the left kidney with metastases to the ribs, vertebral bodies and liver. There were no pulmonary or brain metastases. Microscopic section from the renal tumor showed large polygonal cuboidal cells, the majority of which had an abundant amount of acidophilic cytoplasm. There were occasional areas containing clear cells. The tumor for the most part had an alveolar arrangement, although in some areas there was a tendency to-

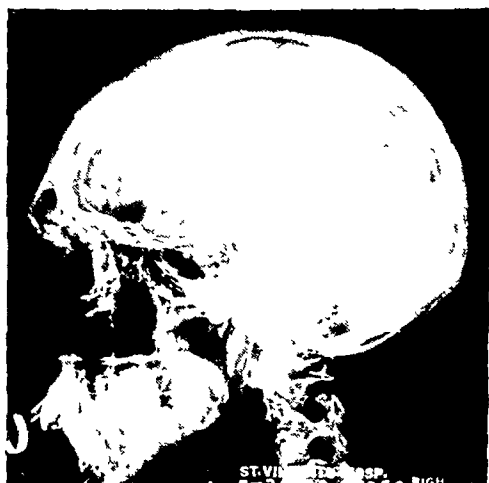


FIG. 2. Roentgenogram of skull showing defect in occipital area.

ward papillary arrangement. There were a few mitotic figures present, although there were numerous giant cells. There were many degenerative changes ranging from pyknosis of nuclei to cystic hemorrhagic degeneration of large areas. The large cysts were lined by a single layer of flat epithelium (fig. 1, B). In the liver metastases, the tumor retained its alveolar form but in the lesion, the tumor cells were solidly packed and the alveolar arrangement was not present.

*Case 2.* The next younger brother consulted his family physician August 20, 1942, fifteen months subsequent to the death of his brother. He was 31 years of age, and complained of headaches of sufficient severity, frequency and duration to interfere with his work as an attorney. Concomitant with the headaches, the patient noticed a small, soft, painless swelling in the right occipital region. Because signs of inflammation were not present, the diagnosis of a wen was made. A local excision was attempted in the physician's office and a profuse hemorrhage was encountered which required pressure bandages for control.

Roentgenograms of the skull disclosed a defect above the suture line on the right side between the occipital and parietal bones. The borders were smooth, consistent with a benign tumor (fig. 2).

To confirm the diagnosis, a biopsy of the tumor was performed. The sections

disclosed small, irregular polygonal epithelial cells, which had a clear to foamy cytoplasm with very small, circular hyperchromatic nuclei. In a few areas, the tumor was solid and the tumor cells packed tightly together, supported by a scarcely perceptible, fine fibrous stroma in which coursed occasional capillaries.

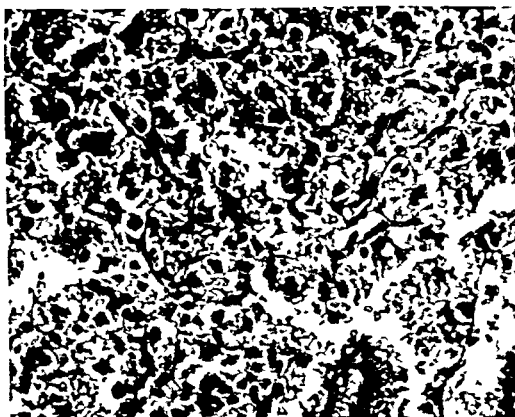


FIG 3. Photomicrograph of tumor from skull showing pseudoalveolar arrangement of tumor cells with foamy cytoplasm and small hyperchromatic nuclei, fine supporting fibroses, stroma and small areas of hemorrhage



FIG. 4. Bilateral pyelogram revealing filling defect in left renal pelvis suggestive of a tumor.

The greater portion of the tumor was hemorrhagic. The hemorrhage occurred between groups of cells giving them an alveolar appearance and occasionally the suggestion of small cyst formations. Elsewhere the hemorrhage had been extensive and the normal structure of the tumor was destroyed and replaced by blood clot. In areas the clot was old enough to have undergone fibrosis and calcification.

The histological diagnosis indicated metastases to the skull from an adenocarcinoma of the kidney (fig. 3).

In view of the bizarre course of his brother's illness, a complete physical examination, including detailed study of the urinary tract, was advised.

The patient was in good physical condition. Over the right occipital and posterior parietal region, there was a tumor 4 by 4 cm. in diameter. A definite pulsation was evident. The temperature was 99 degrees; blood pressure 120 diastolic, 75 systolic. There was no rigidity, tender points or masses present in the abdomen. The prostate was normal in size and consistency. Urinalysis was negative, and the blood count showed 4,780,000 erythrocytes; hemoglobin 94 per cent; leukocytes 8,300.

Cystoscopic examination revealed normal bladder findings with clear jets of urine from each ureteral orifice. Intravenous indigo carmine appeared from each kidney in 6 minutes in good concentration. The separate urine findings were negative. Retrograde pyelograms showed a normal right kidney and ureter. The left renal pelvis showed a filling defect between the upper and middle major calyx with narrowing and elongation of the middle calyx consistent with a cortical renal tumor (fig. 4). Due to the rather advanced lesion in the skull and the uncertainty of a complete removal, left nephrectomy and excision of the cranial lesion were not advised. The occipital tumor increased rapidly in size and at the time of death, one year from the time of diagnosis, it was 16 by 18 cm. in size. The mass was soft, slightly tender, and pulsation was noticeable when touched. A large mass developed in the left flank, which was firm, fixed, consistent with a large renal tumor. Consent for necropsy was not granted.

#### COMMENTS

The phenomenal occurrence of two brothers with distinct metastases due to silent renal adenocarcinoma seems worthy of comment.

The diagnosis in both instances was established by histological evidence of osseous metastases; in one case the rib, the other the skull. Neither patient manifested signs or symptoms of urinary tract disease.

The account illustrates the difficulty of diagnosis of renal malignancy when the predominating symptoms are not related to the urinary tract. It further emphasizes the importance of excluding the kidneys in those instances in which the vague and variable symptoms, known to occur with silent carcinoma of the kidney, exist.

To these obscure and unorthodox manifestations, especially in those of close relationship, might be added the factor of heredity. The presence of the disease in brothers may be a coincidence. Yet the knowledge of its occurrence in one might have been a clue as to its possible existence in the other. Perhaps it is more than chance that in both patients the corresponding kidney was the site of the malignancy.

A re-evaluation of treatment at this time rather strengthens the conviction that an attempt to remove the brain tumor in the second case should have been made.

*Taft Bldg., Hollywood, Calif.*

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## HYPERNEPHROMA IN CHILDREN: REPORT OF TWO CASES

RICHARD H. HEMPSTEAD

*Fellow in Urology, Mayo Foundation, University of Minnesota*

MALCOLM B. DOCKERTY

*Division of Surgical Pathology*

JAMES T. PRIESTLEY

*Division of Surgery*

AND GEORGE B. LOGAN

*Section of Pediatrics, Mayo Clinic, Rochester, Minn.*

Hypernephroma or adenocarcinoma of the renal cortex rarely occurs among children. In 1938 Ladd<sup>1</sup> stated, "We have not encountered a single example of hypernephroma in the last 20 years at the Children's Hospital. From a study of the literature it appears likely that a true hypernephroma is of very rare occurrence in infancy and childhood, and that the term hypernephroma has been used loosely to designate an embryoma of the kidney in many instances."

Bell<sup>2</sup> stated, "About 95 per cent of the carcinomas (adenocarcinomas of the cortex, hypernephroma) develop in persons over 40 years old, and it is doubtful whether this tumor ever occurs in children. The renal tumors of the first decade are nearly all of the Wilms type and very few tumors develop in the second and third decades."

Hellstrom<sup>3</sup> reported a case of hypernephroma in a child 1½ years of age. He stated that the pathologic specimen disclosed fibrosis as a result of roentgen-ray therapy and cells typical of hypernephroma. There had been a marked reduction in the size of the mass after four days of preoperative roentgen therapy which is rather unusual for hypernephroma. In 1905 MacCarty<sup>4</sup> reported a case of hypernephroma in a child 2½ years of age which at necropsy proved to be a tumor arising from the adrenal gland. Melicow<sup>5</sup> reviewed 199 renal tumors and noted that the youngest patient with hypernephroma was 30 years of age. As the literature seemed rather devoid of authentic reports of hypernephroma developing in a child it was thought worth while to describe the clinical and pathologic details of 2 such cases observed at the Mayo Clinic.

### REPORT OF CASES

*Case 1.*—An 8-year-old boy was registered on January 3, 1950, because of abdominal enlargement which had first been noticed by his mother 2 months prior to his admission. The mother stated that except for a chronic, nonproductive

<sup>1</sup> Ladd, W. E.: Embryoma of kidney (Wilms' tumor). *Ann. Surg.*, **108**: 885-902, 1938.

<sup>2</sup> Bell, E. T.: Tumors of the Kidneys. In: *Textbook of Pathology*. Ed. 5, Philadelphia: Lea & Febiger, 1944, pp. 671-673.

<sup>3</sup> Hellstrom, Per: Ein mit gutem Resultat operierter Fall von Hypernephrom bei einem 1½ jährigen Kinde. *Acta paediat.*, **26**: 217-220, 1939.

<sup>4</sup> MacCarty, W. C.: Ein Fall von malignem Hypernephrom bei einem Kinde. *Berl. klin. Wchnschr.*, **42**: 115, 1905.

<sup>5</sup> Melicow, M. M.: Classification of renal neoplasms: Clinical and pathological study based on 199 cases. *J. Urol.*, **51**: 333-385, 1944.

cough of 2 years' duration the child had enjoyed good health. In December 1949, the home physician administered a series of 9 roentgen-ray treatments to the left renal area but these did not grossly alter the size of the mass. During this period the child remained relatively asymptomatic but suffered a loss of 7 pounds (3.2 kg.). The results of physical examination were essentially negative except that the patient appeared chronically ill and presented a large, firm, nontender, smooth mass which filled the left flank and left side of the abdomen. The results of laboratory examinations including urinalysis, studies of serum

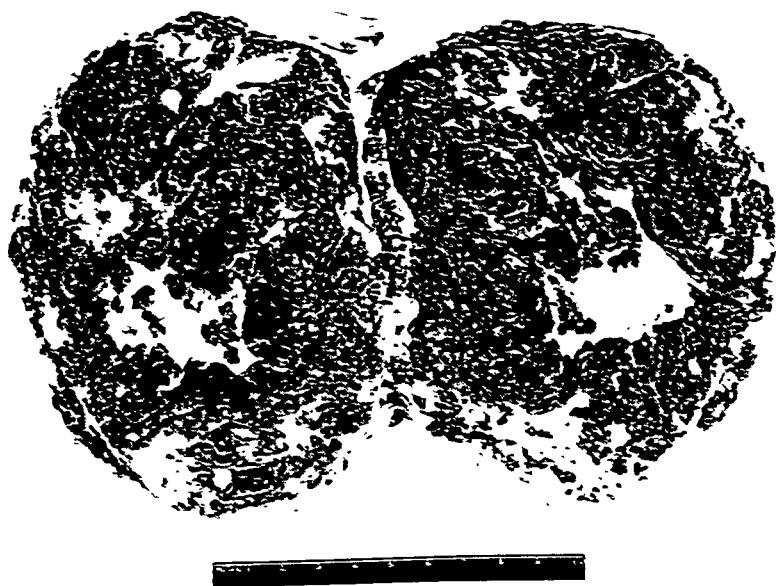


FIG. 1 (case 1). Operative specimen showing large encapsulated hypernephroma involving lower pole of left kidney.

and a blood smear, determination of sedimentation rate and hemoglobin readings were within normal limits. Roentgenograms of the thorax did not reveal evidence of any abnormality. An excretory urogram revealed a large mass in the left upper abdominal quadrant and a calyceal deformity of the left kidney which was consistent with an expanding intrarenal lesion.

At operation on January 17, 1950, performed through a left rectus incision, a large neoplasm was removed from the left kidney. The pathologic specimen weighed 1,050 gm. The lower pole of the kidney was expanded in a globular fashion by an encapsulated solid tumor which measured 15 by 15 by 12 cm. The capsule of the kidney was rather tense over the surface of the tumor but was not invaded. On section the tumor appeared as a degenerating, necrotic yellowish mass which had the gross characteristics of hypernephroma. The tumor invaded

the renal pelvis and peripherally it was adherent to the renal capsule (fig. 1). Microscopically, the picture was that of large, polygonal and, for the most part, clear cells disposed in alveolar formations with deviation to a papillary archi-

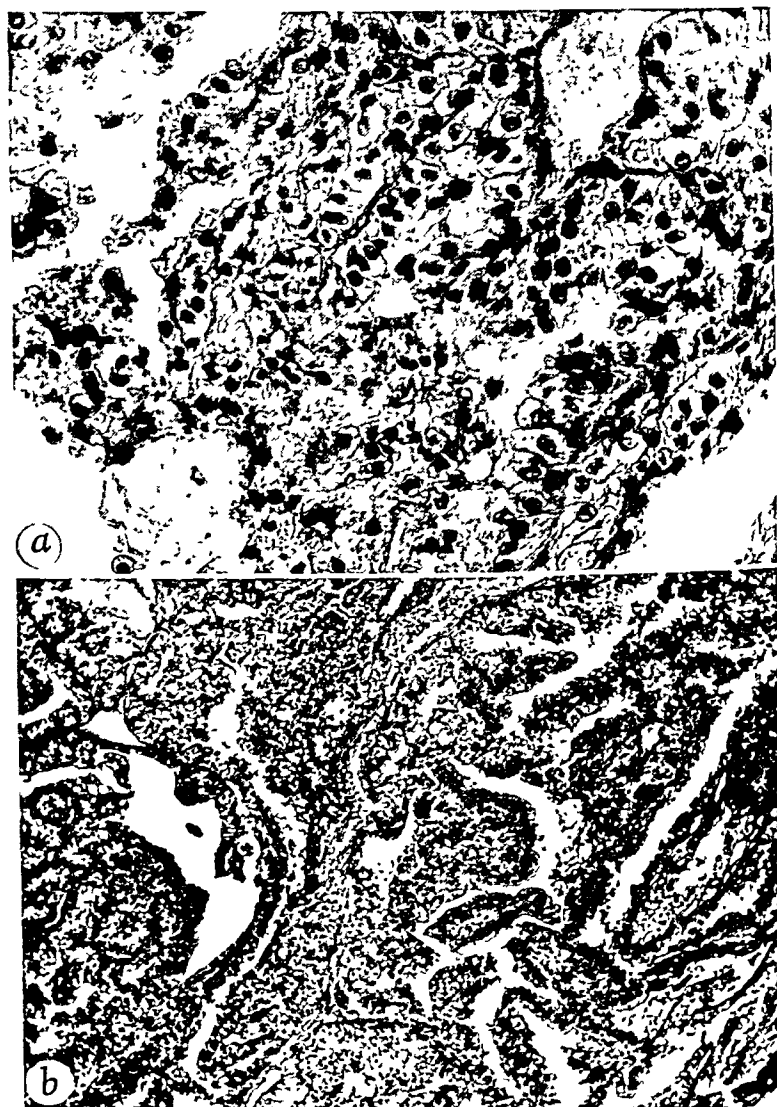


FIG. 2 (case 1). *a*, Alveolar arrangement of large clear epithelial cells is characteristic of hypernephroid carcinoma (hematoxylin and eosin,  $\times 300$ ). *b*, Papillary architecture herein depicted further supports diagnosis of hypernephroma (hematoxylin and eosin,  $\times 60$ ).

ture in many places (fig. 2, *a* and *b*). The appearance was definitely glandular. Stroma was scanty but surprisingly vascular with areas of hemorrhage occurring in many fields. Focal calcification was a noteworthy feature in many sections. The individual neoplastic cells were large, averaging perhaps two or three times

the size of erythrocytes. Nuclei were large and round with finely granular chromatin and mitotic spindles were easily located. The cytoplasm was large



FIG. 3 (case 1). Presence of fat in tumor cells is shown here by dark staining (hematoxylin and eosin,  $\times 60$ ).



FIG. 4 (case 2). Hypernephroma involving upper pole of right kidney. Note large thrombus within tumor.

in amount and the limiting membrane sharp so that many of the cells had definite polygonal outlines. A certain number of the cells exhibited a fine cytoplasmic granularity, the granules being somewhat eosinophilic. Other cells

possessed clear cytoplasm. Special stains showed moderate to large amounts of fat but many of the granular cells contained only traces (fig. 3). Stains for glycogen also gave positive results.

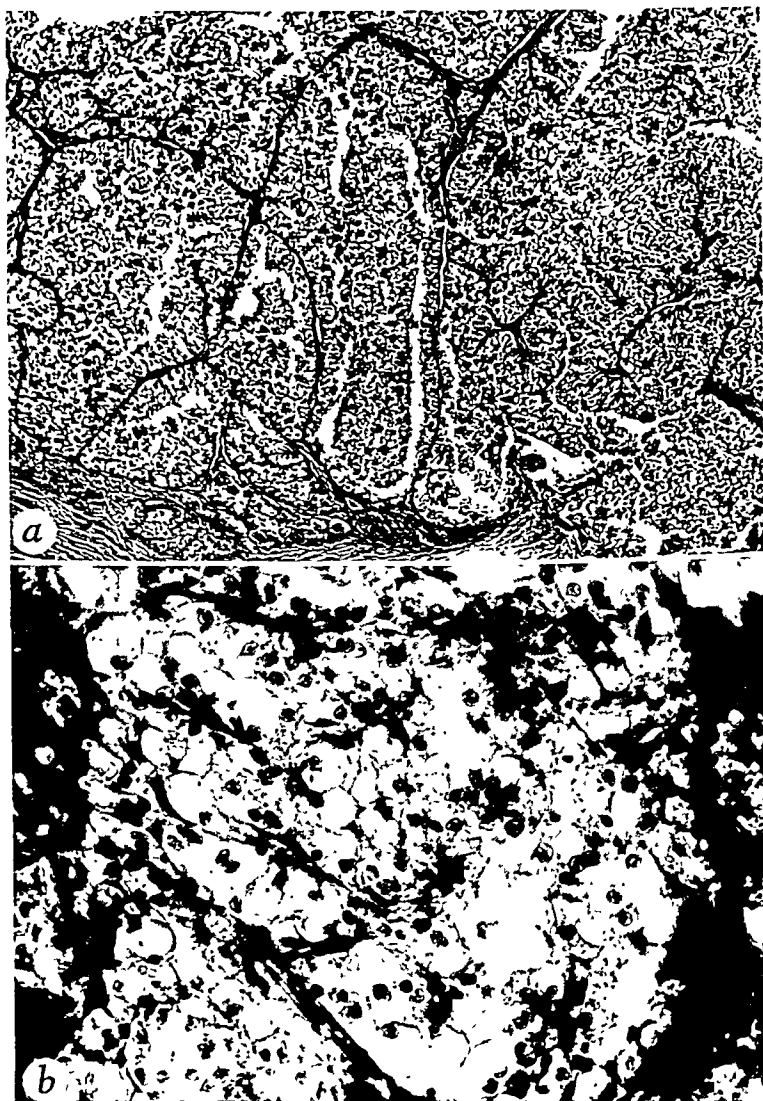


FIG. 5 (case 2). *a*, Fibrous septa divide this microscopic field into a number of alveolar units which are composed of pale-staining polygonal cells. Adenocarcinoma, grade 2, hypernephroma type (hematoxylin and eosin,  $\times 50$ ). *b*, Note details of certain nests of large, clear, lipoid-laden carcinoma cells (hematoxylin and eosin,  $\times 250$ ).

The postoperative course was uneventful and the patient was dismissed from the hospital on the twelfth postoperative day. Subsequent inquiry eight months after operation found the patient to be in excellent general health.

*Case 2.*—A 14-year-old boy was seen in 1929 with a history of intermittent, dull, aching pain in the right upper abdominal quadrant of eight months' dura-

tion. One episode of hematuria had been noted. Physical examination disclosed a movable, nontender mass the size of a grapefruit in the right upper abdominal quadrant. Excretory urography showed that the right kidney was not functioning. Calcification in the right renal area was evidenced roentgenographically. Retrograde pyelographic studies revealed a deformity of the calyces consistent with a renal neoplasm. The results of laboratory examinations were within normal limits.

Surgical exploration revealed a large neoplasm of the right kidney which was removed. The pathologic specimen consisted of the right kidney which weighed 540 gm. and measured 10 by 8 by 10 cm. Gross involvement of the renal veins by tumor was evident (fig. 4). It was estimated that 80 per cent of the renal substance was destroyed. The microscopic picture was essentially the same as that described in case 1 (fig. 5, *a* and *b*)

Postoperatively the patient received 10 hours of treatment with radium and two roentgen-ray treatments. The patient was rather well for about a year at which time metastasis developed and he died within a few weeks.

#### COMMENT

Approximately 80 per cent of primary malignant renal neoplasms are adenocarcinomas of the hypernephroma type; 12 per cent are carcinomas of the renal pelvis; 5 per cent are Wilms's tumors, and the others are leiomyosarcomas, fibrosarcomas, liposarcomas, and so forth.<sup>6</sup> Wilms's tumor is perhaps the commonest primary malignant abdominal neoplasm of children but its occurrence among adults is rarely observed. Conversely, as already pointed out, hypernephroma rarely affects persons who are less than 30 years of age. It is extremely unusual for malignant renal neoplasms of any sort to develop in persons between the ages of 10 and 30 years, and in the literature we have not found any unquestioned examples of hypernephroma among children. One might well inquire into the possible reasons why age is such a decisive factor in the genesis of these growths.

Hypernephromas are regarded as arising from renal tubular epithelium and usually attain considerable size prior to producing symptoms. In cases in which they have been discovered in incipient stages the difficulty in separating them from renal adenomas has been so great that the adenomas have been regarded as being important precursors.<sup>7</sup> The development of renal adenomas is in itself a slow process, often based on arteriosclerotic destruction of glomerular units with secondary cystic dilatation and proliferation of their associated tubular apparatus. Such arteriosclerotic changes are a hallmark of advancing years and are rarely observed in childhood. Pathologically as well as clinically, the change from adenoma to metastasizing hypernephroma is slow and insidious. Bell's<sup>8</sup> experience with a metastatic lesion which measured 1.5 cm. in diameter is

<sup>6</sup> McDonald, J. R. and Priestley, J. T.: Malignant tumors of the kidney: Surgical and prognostic significance of tumor thrombosis of the renal vein. *Surg., Gynec. & Obst.*, 77: 295-306, 1943.

<sup>7</sup> Cabot, Hugh and Middleton, A. W.: The relation of so-called adenoma of the kidney to carcinoma of the kidney. *Tr. Am. A. Genito-Urin. Surg.*, 31: 91-105, 1938.

<sup>8</sup> Bell, E. T.: Tumors of the Kidneys. In: *Renal Diseases*. Philadelphia: Lea & Febiger, 1946, pp. 411-428.

unique in this regard. He also observed metastasis of only 7 per cent of hypernephromas which were 5 cm. or less in diameter. The figure reached 83 per cent, however, when growths measuring 10 cm. or more were considered.

We suggest that a hypothesis for the rarity of hypernephromas among children be based on the following 3 factors: 1) the observed infrequency of renal adenomas prior to the degenerative years, 2) the low growth potential of these adenomas and 3) the tendency for hypernephromas which are so engendered to remain as silent menaces until considerable size has been attained.

#### SUMMARY

Two examples are recorded of renal adenocarcinomas of hypernephroma type, occurring in children. We have been unable to find reports of comparable cases in the literature.

The theory of origin from renal adenomas has been offered to explain the infrequency of hypernephromas during childhood since the formation of these adenomas appears to be related to aging processes.

## RETROPERITONEAL LIPOMA IN CHILDREN: REPORT OF CASE AND REVIEW OF LITERATURE

B. MARVIN HARVARD

*From the Department of Urology, Ochsner Clinic and the Division of Urology, Tulane University of Louisiana, School of Medicine, New Orleans*

Retroperitoneal lipomas are uncommon tumors reported to manifest themselves clinically with greatest frequency in the fifth and sixth decades of life. Rarely do they reach clinical proportions in a child. Only 8 cases of retroperitoneal lipomas in children have been found in the medical literature. (Bork; Chown; Dalziel; Kay; Kretschmer; Neumann; Vautrin.) The case to be described brings the total number of recorded cases to nine.

### CASE REPORT

B. A. P., a white girl aged 2 years and 6 months, was admitted to Touro Infirmary June 4, 1949 because of earache, backache and fever of 24 hours' duration. She had a protuberant abdomen.

Her developmental history was normal. No other members of the family had had protuberant abdomens. Except for a frequent infection of the upper respiratory tract accompanied by fever and earache, the patient had been well. The mother stated that the child's abdomen had always been large. The patient had never complained of discomfort and had shown no signs of gastro-intestinal disturbance. She had a good appetite and normal bowel habits and appeared to the mother to be not remarkably different from her other children.

Physical examination revealed a normally developed, placid girl weighing 30 pounds, with slightly flushed facies. Her temperature was 102F, pulse rate 110 and respirations 20 per minute. Both eardrums were inflamed. The tonsils were enlarged and showed purulent folliculitis. The cervical nodes were palpably enlarged. The heart and lungs were normal. The abdomen was considerably protuberant, obviously more so on the left. A firm, smooth, movable, nontender mass filled the left half of the abdomen from the costal margin to the crest of the ilium. The percussion note over it was flat and no bowel sounds could be heard over the left side of the abdomen. The remainder of the physical examination revealed no abnormalities.

The blood count indicated mild leukocytosis and mild anemia. Examination of the urine and feces showed nothing remarkable. A roentgenogram of the chest was normal.

Twenty-four hours after the first injection of penicillin was given for the otitis media, the temperature became normal. A week later the child had another infection of the upper respiratory tract, which again responded to administration of penicillin.

On presumption that the mass in the abdomen was a large Wilms's tumor, investigation was begun with excretory urography. A plain roentgenogram of the abdomen showed a mass approximately 8 by 15 cm. on the left side of the abdo-



men displacing the small intestine upward and to the right. It contained no calcified areas and was separate from the spleen, which appeared to be normal. The outline of the left kidney could not be identified. That of the right kidney was normal. The contrast medium appeared promptly and in normal concentration in each renal pelvis. The left pelvis and the calyces were displaced upward and medially and appeared to be rotated 90 degrees upon their anteroposterior axis. The remaining portions of the system visualized appeared normal except for rotation and displacement of the left kidney. The ureters were not visualized.



FIG. 1. A, left retrograde pyelo-ureterogram showing renal and ureteral displacement. B, left lateral view.

Retrograde pyelo-ureterograms (fig. 1) showed, in addition to these observations, the left ureter to be deviated past the midline. No actual encroachment upon or distortion of the calyces was seen. The left kidney appeared to be sitting on top of a large mass.

A diagnosis of retroperitoneal tumor was established. Because of the possibility of its being a Wilms's tumor, a preoperative course of roentgen ray was given without appreciable change in the size of the tumor.

At operation the left kidney was seen to be pushed upward, forward and medially by a large, separate, encapsulated, fatty, retroperitoneal mass. The tumor, which was attached to its upper and lower poles by thin pedicles connected to the paravertebral connective tissue, was easily removed.

The tumor itself was a yellowish brown, encapsulated mass measuring 16 by 16 by 18 cm. The cut surface was pale yellow and homogeneous except for a central

gray necrotic area about 5 cm. in diameter. The microscopic picture was that of well differentiated fat cells arranged around small capillaries with areas of fat necrosis. The tumor was histologically benign.

Three months following removal of the tumor the baby was completely well. Urograms at that time showed that the left kidney had resumed its normal position.

#### REVIEW OF LITERATURE

To my knowledge the earliest recorded case of a retroperitoneal lipoma in a child is that of Lauwers in 1891; he successfully removed a pure lipoma weighing 6 kg. from the root of the mesentery in a boy 7 years old. Abdominal distention and prominent superficial veins had been present since early infancy.

Dalziel reported the case of a girl aged 8 years who presented the picture of intestinal obstruction with periodic vomiting and constipation as well as prominent tortuous superficial abdominal veins. She died "in syncope" before the initial incision was completed but the tumor was found to be a pure lipoma weighing 13 pounds.

Bark's patient, a girl 1 year old, is the youngest on record to have been operated upon. She had had a distended abdomen since early infancy. A pure lipoma "the size of the child's head" was removed successfully from the perirenal fat on the right. She was reported to be normal eighteen months later.

Neumann removed a pure lipoma weighing 7 pounds from the left retroperitoneal space of a boy nearly 4 years old. The only manifestation, swelling of the abdomen, had been present for about 1 year. The child was reported to be well five months following removal of the tumor.

In Kay's patient, a boy 4 years old, the symptoms began with sudden onset of pain in the lower part of the abdomen and acute urinary retention. Laparotomy revealed a retroperitoneal fibrolipoma "the size of an orange" arising from the region of the sacrum. In addition there was a "loculus" of the bladder (probably a diverticulum) which with the pressure of the large tumor accounted for the urinary symptoms. The child was reported well 2 years later.

Vautrin described the case of a girl 5 years old who had had abdominal swelling, prominent abdominal veins and constipation since she was 6 months old. He successfully removed a pure lipoma weighing  $7\frac{1}{2}$  kg. from the root of the mesentery.

Kretschmer reported the only malignant retroperitoneal tumor in a child that I have been able to find in the literature. The patient, a girl aged 2 years, had a swelling on the right side of the abdomen for 2 weeks. In addition, anorexia and alternating constipation and diarrhea were noted. The retroperitoneal lipoma, which measured 105 cm. by 90 cm. by 90 cm., was successfully removed.

Chown reported successful removal of a lipomyxoma arising from the pelvis and weighing 2041 gm. in a girl  $3\frac{1}{2}$  years old. She had had a large abdomen for at least 3 years. She was reported well 5 years later.

The etiology of lipomas is unknown. According to Ewing, "congenital tissue predisposition seems to be an essential factor in the origin of most lipomas. This

predisposition may take the form of a disturbance of development of the fat tissue." Support is lent to this view by evidence that the tumors were present in earliest infancy in 5 of the 9 reported cases. Lipomas do not usually grow rapidly. It is not inconceivable then to suppose that some of the tumors noted in adulthood had their beginnings in small, inconspicuous, slowly growing tumors in infancy. According to Bell, lipomas occasionally grow with certain rapidity leading one to suspect malignant change. It may possibly have been just such activity that made two of these tumors appear suddenly.

Retroperitoneal lipomas are encountered twice as often in females as in males. Six of the 9 reported cases were in girls and 3 in boys.

The ages of these children ranged from one to 8 years. There are no reported instances of patients in the second decade of life operated upon for retroperitoneal lipomas. Such tumors begin to manifest themselves clinically in the last years of the third decade and are encountered in greatest numbers in the fifth decade.

Most pathologists, although reporting the majority of these tumors to be histologically benign, nevertheless inject a note of caution. It has been the experience of those dealing with these tumors in adults that many have shown foci of frank malignancy at the initial examination. It is believed by some that a much higher percentage of these foci of sarcomatous change would be discovered if more thorough study of the tumor were to be carried out. In addition, the recurrence rate of the benign lipoma is high.

The points of origin of the tumors in this series paralleled closely those reported in adults. According to Mayo and Dixon, 80 per cent arise in the abdomen and the remainder arise in the pelvis. McLaughlin and Sharpe considered the perirenal site as the commonest point of origin. In the present series one was reported to have arisen from the perirenal fat, 2 from the root of the mesentery, 2 from the pelvis, one from the paravertebral fat and in 3 the origin was not mentioned.

In diagnosing these tumors one is confronted with the obvious differentiation between intraperitoneal and retroperitoneal tumors. Symptomatically, the history is simply that of progressive abdominal enlargement with or without accompanying symptoms related to extrinsic pressure to various intra-abdominal viscera. Radiologically, pure lipomas are said to be characterized in all cases by radiolucency of the involved area and visceral displacement. In this latter phase urography is of inestimable value. Characteristically, pyelo-ureterograms will reveal ureteral displacement as well as renal displacement and rotation. Depending upon the position of the tumor there may or may not be associated hydronephrosis or calyceal distortion.

Treatment is, of course, surgical removal of the tumor. If the tumor is encapsulated, such as in the case herein reported, the operation presents no particular technical difficulty. However, many of these tumors are not encapsulated and present multiple ramifications. Because of their intimate association with retroperitoneal viscera it is frequently difficult to remove them entirely. It has been the experience of many that after such incomplete operations the tumor not only recurs but becomes increasingly more malignant both histologically and anatomically.

## SUMMARY

Retroperitoneal lipomas of clinical proportions rarely occur in children. The ninth case is presented and the 8 previously reported cases are briefly described.

*New Haven Hospital, New Haven, Conn.*

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## ECTOPIC OPENING OF URETER INTO SEMINAL VESICLE

C. M. PASQUIER, JR. AND R. K. WOMACK

*From the Veterans Administration Hospital, Shreveport, Louisiana*

The following case report is thought to represent the eighth reported instance of the diagnosis during life of this rare but interesting anomaly.

An investigation of the urinary tract in a young white man complaining of enuresis disclosed cystoscopic findings strikingly similar to those recently described by Hamilton and Peyton. Further study, as carried out by these two authors, led to the diagnosis of ectopic opening of the right ureter into the right seminal vesicle.

Riba, Schmidlapp and Bosworth reviewed the literature in 1946 and found published reports of this anomaly in 32 autopsy cases and four clinical cases. They added a case of their own, diagnosed clinically, thus bringing the number of cases diagnosed during life to a total of five. The sixth clinical case was reported by Engel in 1948, and the seventh by Hamilton and Peyton in 1950.

The embryological origin of anomalies of this type has been clearly explained by Campbell. Between the fifth and sixth weeks of fetal life the ureteral bud and the wolffian duct are attached to the urogenital segment of the cloaca. Later, these two structures are separated as the ureteral orifices are carried upward into the lateral angle of the trigone. Any failure of this normal separation might result in abnormal opening of the ureter into any of the structures derived from the wolffian duct, including the seminal vesicle.

### CASE REPORT

A 26 year old white man was admitted to the Veterans Administration Hospital, Shreveport, La. on January 16, 1951, complaining of enuresis. The latter condition had existed since birth and he had received a discharge from the Army because of it. No other symptoms were referable to the genito-urinary system and the medical history was otherwise negative except for the fact that the patient's father and one of his brothers had a history of enuresis. Positive findings on physical examination were limited to the following points. Upon inspection of the genitalia there appeared to be a double external urinary meatus. One of these was placed in the usual location at the end of the glans penis, the other was ventral and slightly proximal to the former. However, more careful examination indicated the ventrally placed meatus to be the functioning one. The other terminated blindly several millimeters proximal to its opening. The prostate was normal in size, shape and consistency. A suggestion of some cystic enlargement was noted on rectal examination in the region of the right seminal vesicle. The blood count on admission showed 14 gm. of hemoglobin, 4,920,000 red blood cells,

Sponsored by the Veterans Administration and published with the approval of the Chief, Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Accepted for publication July 30, 1952.



FIG 1. *A*, excretory urogram showing large left kidney. No evidence of right kidney. *B*, ureteral catheter coiled within intravesicular mass after latter had been punctured with electrode. *C*, dilated, tortuous right ureter demonstrated after injection of catheter. *D*, right seminal vesiculogram showing communication between seminal vesicle and right ureter.

10,200 white blood cells, 71 per cent neutrophils, 25 per cent lymphocytes, 1 per cent monocytes and 3 per cent eosinophils. Urinalysis, including microscopic examination of the sediment, was entirely normal. Serology was negative.

Complete urological investigation was planned because of the history of enuresis and the presence of the above described genital anomaly. Excretory urography demonstrated a very large renal shadow on the left with good function and normal filling of the pelvis and calyces on this side (fig. 1, A). However, there was no evidence of a renal shadow on the right or excretion of contrast medium even on delayed films.

Cystoscopy was performed January 25, 1951. The verumontanum was moderately enlarged and inflamed. Considerable granulation tissue was noted in the posterior urethra. On the floor of the bladder, just proximal to the vesical neck, a large globular mass, estimated to be about 3 cm. in diameter, was observed. It appeared to arise from the right side of the trigone. The overlying mucosa had a normal appearance. On first impression it was thought that the mass might be a ureterocele. However, careful search, even after the administration of indigo carmine, failed to disclose any evidence of a right ureteral orifice. The left orifice was normal in position and appearance. The posterior urethra was inspected thoroughly for an ectopic ureteral orifice but none was found. Several days later, cystoscopy was repeated, again searching carefully for a right ureteral orifice after injecting indigo carmine and again none was found.

Because the cystoscopic findings so closely coincided with those described by Hamilton and Peyton in their case report, it was decided to proceed along the same lines of investigation followed by them in the work-up of their case. Accordingly, on February 7, 1951, cystoscopy was performed under spinal anesthesia and the previously described globular mass in the bladder was punctured with a ball-point electrode. Thick, brownish material began to drain out as soon as the opening was made. A 5F whistle-tip ureteral catheter was inserted into this opening and passed a distance of 25 cm. There was a rapid drip of thick, brownish, odorless fluid from the end of the catheter which was then aspirated, removing about 25 cc of material. Microscopic examination of the latter showed innumerable dead sperm but no pus cells. Cultural studies were negative for pyogenic organisms and acid-fast bacilli. A plain urogram showed the ureteral catheter coiled concentrically, apparently within the punctured cystic mass (fig. 1, B). Skiodan (12 cc of a 40 per cent solution) was injected through the catheter and another picture made (fig. 1, C), demonstrating a structure resembling a dilated and tortuous ureter extending upward from the region of the coiled catheter to the lower margin of the right sacro-iliac articulation.

On March 14, 1951, the patient was given a spinal anesthetic, and the right vas deferens was exposed in the scrotum and catheterized with a 4F olive-tip ureteral catheter. A seminal vesiculogram was obtained by injecting 10 cc of 40 per cent skiodan into the catheter and very clearly demonstrated a communication between the right seminal vesicle and right ureter (fig. 1, D). The latter was outlined as high as the fourth lumbar vertebra, appearing to end blindly at that point.

Operation was performed on March 23, 1951. The lower right ureter was exposed through a suprapubic midline incision and found to be markedly dilated and tortuous. Dissection was carried downward, behind the bladder, visualizing the upper portion of the right seminal vesicle which also appeared quite dilated. In attempting to develop dissection further so as to expose the point of junction between the ureter and seminal vesicle, the former was accidentally detached from its lower insertion before this point could be reached. A ligature was placed on the detached end of the ureter which was then freed proximally as far as possible. The right seminal vesicle was removed, and upon completion of this step, it was noted that a small opening was present in the base of the bladder. This was closed in layers with chromic catgut. The abdominal wound was repaired and the patient placed on his left side. The usual curved lumbar incision was made in the right flank. A right kidney could not be found. The ureter was identified lower in the wound and then traced proximally, terminating in a small, round mass, about 3 cm. in diameter, thought to be a hypoplastic kidney. The latter structure and the entire right ureter was removed. The wound was closed in layers.

The postoperative course was uneventful, both wounds healing by primary intention. The enuresis did not improve; however, this was not surprising in view of the fact that psychiatric consultation obtained preoperatively had demonstrated an intelligence quotient of 71 and a mental age of 11. Moreover, it should be stated at this point that operation was performed with little or no hope of curing the condition of enuresis, but rather because it was believed that later trouble could be anticipated since communication had been produced between the bladder, the seminal vesicle and the dilated, blindly-ending right ureter.

The pathological report on the surgical specimens stated that the structure at the proximal end of the ureter contained varying numbers of tubules, some of them cystic, thought to be renal tubules. No glomerular structures were found. The ureter averaged 0.9 cm. in diameter and the muscularis showed marked hypertrophy. The seminal vesicle was cystic and the walls showed muscular hypertrophy.

#### SUMMARY

A case of ectopic opening of the right ureter into the right seminal vesicle is presented. The kidney on the corresponding side was hypoplastic. This is the eighth reported case of this anomaly diagnosed clinically.

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## FILLING DEFECTS OF URETEROGRAM CAUSED BY A VARICOSE URETERAL VEIN

MICHAEL H. BERMAN AND HERBERT COPELAND

*From the Urological Section and Radiology Service, VA Hospital, Bronx, New York*

The purpose of this communication is to describe a previously unreported cause of deformity of an ureterogram which produced changes closely simulating filling defects due to intraluminal papillary tumors of the ureter.

L. J. C. (BVAH No. 117 621) a white man, 57 years of age, was referred from another Veterans Administration Hospital on July 22, 1949 for observation for recurrent multiple papillomas of the bladder, the first diagnosis of which was made 15 years prior to this admission.

Physical examination at the Bronx Veterans Administration Hospital revealed a poorly nourished man in no acute distress. No general physical abnormalities were noted. Excretion urograms showed normal kidney pelves and calyces. The right ureter was normal. The left ureter showed well defined indentations or filling defects on the medial aspect of its upper five centimeters. On cystoscopic

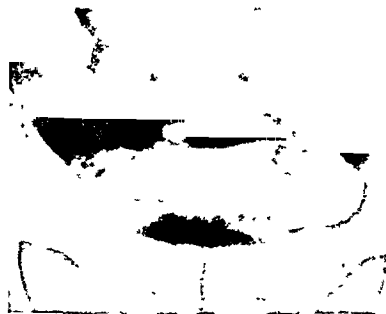


FIG. 1. Filling defect in left post trigonal area near left ureteral orifice.

examination, the bladder was found to be the seat of four small papillary tumors found on the lateral wall (fig. 1). Biopsy specimens were subsequently reported as "benign papilloma." Catheters were introduced into each ureter to 26 cm. without encountering obstruction and retrograde instillation of dye demonstrated the same filling defects in the proximal position of the left ureter as were seen in the excretion urograms (fig. 2, A).

On August 1, 1949, the four papillomas were destroyed by electrocoagulation under spinal anesthesia. Ten days later, in order to re-evaluate the left ureter, a No. 10 Braasch bulb catheter was again introduced into the left ureter and a ureteropyelogram done, demonstrating persistent filling defects in the proximal ureteral segment.

On August 26, 1949 the left ureter was examined surgically. The left kidney and upper two-thirds of the ureter were freed from surrounding structures. The medial and posterior aspects of the ureter were indented by a curving, markedly adherent vascular structure, approximately half as wide as the ureter. Except for invagina-

tions of the ureter by this varix, the rest of the ureter appeared normal in all respects. Similarly, other peri-ureteral tissues did not reveal any abnormality. An attempt to trace this vein was unsuccessful; however, it appeared to originate from venous structures about the midportion of the ureter and to empty into a vein coursing on the anterior surface of the pelvis.

The size, position and extent of this varicosity made the probability of its being the cause of the ureteral defects at once evident. This probability was strengthened when palpation of the kidney pelvis and upper ureter did not reveal any masses and when inspection and palpation of the pelvic and ureteral lumen through a wide incision did not show any growths. A 10F catheter was introduced into the ureter and passed without obstruction into the bladder. Again palpation over this catheter did not reveal any intraluminal masses. The spermatic vein was



FIG. 2. A, filling defects in medial aspect of proximal ureteral segment. B, retrograde ureteropyelogram taken 9 months following surgery illustrates normal caliber of left ureter.

identified and found to be normal. The varicosity was ligated with fine catgut suture at its end near the pelvis of the kidney and incised. No attempt was made to excise the vein. The opening in the pelvis and ureter was sutured, the kidney replaced, and the wound closed in layers. The postoperative course was uneventful. A retrograde pyelogram, performed prior to his discharge 14 days later, revealed the absence of previous intraluminal defects. A normal appearance of the upper ureter was evident on pyelo-ureterograms taken 9 months following surgery (fig. 2, B).

#### DISCUSSION

The presence of papillomatous lesions in the bladder associated with persistent filling defects in the ureter demands investigation of the upper urinary tract. If, as is most likely in such cases, the ureter is the site of tumors, radical surgery must be performed. Knowledge of these facts led to the fallacious conclusion that the

clinical picture of this patient could be explained on the basis of upper ureteral papillomas with similar tumors in the bladder.

At operation, a varicose vein involving the upper third of the ureter was found. This was adherent to the ureter within the peri-urethral sheath and ran an irregular, winding course along its medial aspect. Furthermore, intramural examination of the renal pelvis and upper ureter through an incision showed no abnormality. Antegrade passage of a 10F ureteral catheter through the ureter and into the bladder failed to encounter obstruction. Ligation of the varicosity was followed by a normal ureterogram.

No explanation for the existence of the varicosity was apparent. Possibly changes in the involved ureteral vein similar to those changes in the internal spermatic vein which lead to formation of a varicocele, might be applicable in this instance. In the case of varicocele, valvular incompetence, length of the vein and right angle insertion into the renal vein are considered causative factors. Similar causes may have played a role in this instance but could not be demonstrated.

The differential diagnosis of filling defects of the ureter such as were present in this case must include ureteritis cystica; tuberculous ureteritis; chronic, nonspecific ureteritis; ureteral tumors both benign and malignant; and para-aortic lymph node enlargement causing extrinsic pressure on the ureter. In ureteritis cystica a greater degree of ectasia usually is noted. Increased irregularity and involvement of the lower two-thirds of the ureter would be expected. The scalloping effect would not be limited to the medial aspect. Also, ureteritis cystica is usually bilateral. Tuberculosis of the ureter involving the subepithelial tissue characteristically produces irregular narrowing of the lumen with zones of dilatation above the partial obstructions. The localization of the defects to the medial border as well as their suggestive extrinsic nature might tend to rule out papilloma as well as other benign ureteral neoplasms. Para-aortic nodes when large enough to produce pressure effect on the ureter would not be expected to produce such discrete scalloping.

In retrospect, it is evident that the source of the multiple indentations in the upper ureter of this patient was extrinsic rather than intrinsic. An analogy may be drawn between this entity and similar extraluminal indentations of the oesophagus caused by varices, noted roentgenographically.

#### CONCLUSION

A case report in which varicosities of the ureteral veins exerted extrinsic pressure and produced filling defects in the ureteral lumen is presented. Since these changes simulated the filling defects in ureterograms caused by ureteral papillomas and since they were found in a patient who had papillomas in his bladder, the correct interpretation of the roentgenological picture was not made before operation. The urologic and roentgenographic findings and the differential diagnosis are briefly discussed. This is believed to be the first report of such an entity.

## MEGALO-URETER AND RELATED CONDITIONS IN CHILDREN: REPORT OF SIX CASES

JOHN K. ORMOND

*From the Henry Ford Hospital, Detroit, Mich.*

I wish to show you 6 cases of ureteral dilatation in children. Three of these I believe to be true instances of megaloureter; one is definitely on an obstructive basis; and the other two I cannot classify satisfactorily. These 6 cases are of interest because of their course and because of the type and results of the treatment they received.

### CASE REPORTS

*Case 1.* Henry Ford Hospital No. 103487. This patient came to our attention in 1928. He was then a handsome, vigorous, healthy appearing boy 6 years old and was brought to the Pediatric Department because of enuresis. On examination pus was found in the urine and the phenolsulfonphthalein test showed 23 per cent in 2 hours. He was found to have over 500 cc residual urine and a cystogram was made (fig. 1). Cystoscopy disclosed a moderate degree of trabeculation; widely open, but not rigid ureteral orifices; no diverticula. No valves or other obstruction of the prostatic urethra were found.

About this time, Hinman had first described an operation for megaloureters. He recommended nephrostomy, straightening of the ureter, excision from the lower end to shorten the ureter, with re-implantation into the bladder. I advised that this operation be performed, but after consultation, the parents decided against any operation. We were able to follow this patient's career until his death about 12 years later. I am indebted to Dr. Robert McArthur of Detroit for the details and for the pictures which I shall show.

The patient developed normally; he was an athletic, social and intellectual leader in high school and college. The pyuria persisted all his life. This was before the era of antibiotics. In the middle of his sophomore year, when he was 19 years old, he one day found that his pencil dropped from his hand. He immediately took a train to Detroit, arrived at home at 7 p.m., was in coma by 11 p.m., and died the next day. An autopsy was done and I show you now the pictures of his urinary tract. Outside the urinary tract no abnormalities were found (fig. 2). As you can see, the bladder while somewhat thickened, is not particularly enlarged and there is no obstruction at the orifice. The ureters are hugely dilated and tortuous and the kidneys are reduced to mere shells.

If the patient had undergone an operation, would the result have been any better? Probably not. This boy was a source of pride and joy, tempered with anxiety, to his parents for 19 years. He himself did not realize his condition and lived a happy and successful life and died without pain or long drawn out illness.

*Case 2.* A baby girl was first seen at the age of 21 months; she was sent by her physician with a history of recurrent attacks of fever and pyuria during the past 3 months, and brought with her a cystogram which showed reflux up both ureters. She was a small but healthy appearing child.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 19, 1952.

Cystoscopic examination showed a somewhat enlarged but not trabeculated bladder with no sign of any obstruction at the orifice, and with a widely open left ureter, and a normal appearing right one. Pyelograms and a cystogram



FIG. 1



FIG. 2

showed reflux up the left ureter into a dilated pelvis; no reflux on the right but considerable dilatation of the upper two thirds of the right ureter and some dilatation of the pelvis. According to the indigo carmine test, the function of the right kidney was almost normal, but on the left it was diminished.

Our impression was that we had here an early case of megaloureter: one in which treatment would be indicated, if ever. We had been impressed by the frequent association of megaloureter and megacolon, and Svenson had published his work on the cause and treatment of the latter condition, and we decided to try a somewhat similar treatment to the ureters of our patient. Operation was done first on the left side in the following manner: A rubber catheter, No. 12, was passed up the ureter, and the ureteral orifice circumcised and the intramural portion dissected free. The ureter was then drawn down into the bladder and  $1\frac{1}{2}$  inches of its lower end excised. A No. 8 catheter was then substituted for the No. 12 and the caliber of the ureter reduced by excision of a ribbon of ureteral wall as far up the ureter as we could reach, and the ureter repaired about the catheter.



FIG. 3

Convalescence was uneventful. Four months later cystoscopy showed the left ureteral orifice widely open, drawn back of and above its former position. The right orifice showed larger than before and cystogram showed apparent anatomical improvement on the left (or operated) side but definite reflux and increased dilatation on the right. A month later cystoscopy corroborated this. Because of the apparent improvement in the left and apparent deterioration on the right, the same operation was done on the right as had been done on the left. Again convalescence was uneventful. Cystogram 5 months later showed both ureters dilated, possibly a little more than before, but the pelves showed no further dilatation. Cystogram 5 months after this showed much the same picture.

She has had several sessions with fever and pyuria since. Her mother writes that she is growing and seems very well between attacks.

The best we can say in this case is that apparently the operation did no harm.

*Case 3.* Henry Ford Hospital No. 583114. When first seen the patient was 2 years old, well enough grown but rather pasty in appearance. Her urine was milky with pus, and she had had frequency and polydipsia for more than a

year. Her systolic blood pressure was 140, hemoglobin 10.1 gm. per 100 cc of blood, nonprotein nitrogen 51. Urinalysis disclosed much pus and albumin and a specific gravity of 1.008.

Cystoscopy and cystograms resulted in a diagnosis of megalo-ureter, with far advanced destruction of both kidneys, the right being more damaged than the left. The bladder showed some hypertrophy and the ureteral orifices were widely open, but no obstruction could be demonstrated (fig. 3, A).

At the first operation a left nephrostomy was done and the redundant upper part of the ureter excised with re-anastomosis of the cut ends. So much improvement in her condition followed this that the same operation was done on the right side 10 weeks later. The nephrostomies closed without undue delay and for a time she was markedly improved. The urine became grossly clear, though it never became entirely free from pus cells.

Later her condition deteriorated and a third operation was done. The lower ends of both ureters were excised; the caliber of each ureter was reduced by excising a ribbonlike longitudinal strip with repair of the ureter about a No. 12 catheter, and the lower ends then drawn down into the bladder through the original site of insertion.

Healing took place without undue delay, and 11 weeks later a cystogram showed extensive reflux bilaterally into large ureters and into the renal pelves (fig. 3, B). This looks like a failure. However, 11 months later (last December) she was in surprisingly good condition, with normal weight and height and with clear urine. Urinalysis showed specific gravity 1.008; albumin, a faint trace; no sugar and an occasional pus cell in the centrifuged specimen.

The treatment was unorthodox in that both ends of both ureters were excised, apparently with no bad result. We have certainly done this child no harm, for she is in far better condition than when we first saw her. How permanent this improvement may be is open to grave doubts, remembering the years of vigor of the boy described in the first case report.

*Discussion.* I believe all three of these are cases of true megalo-ureter. We may define megalo-ureter as a congenital condition in which are found dilated atonic ureters, with reflux on filling the bladder; with consequent pelvic dilatation not in proportion to the ureteral dilatation; with no evidence of organic obstruction in the ureter, bladder or urethra, past or present; and with no associated neurological condition such as meningocele or spina bifida.

As we review the literature, two things stand out: 1) many cases reported as megalo-ureter are really hydro-ureters on an obstructive basis; and 2) true megalo-ureter is often associated with megacolon (Hirschsprung's disease) and mega-esophagus. This association suggests that they may have a similar etiology.

The names most prominently connected with the condition are: Saintu, Papin, Legueu, Braasch, Ockerblad, Hepler, Hinman, Granville Crabtree, Eisenstaedt, Caulk, Meredith Campbell and E. W. Campbell.

Five years ago E. W. Campbell read before this society and in this place a paper on megalo-ureter. I quote from his conclusions: "Evidence has been given

to prove the existence of two distinctly different types of congenital ureteral dilatation, which are now termed megalo-ureter. It is suggested that the term megalo-ureter should be reserved solely for the enormous congenital ureteral dilatations with atonic ureteral orifices and dilated renal pelvis, the type originally described by Saintu.

Huge congenital dilatations of the ureter with normal terminal spindles should be called congenital hydro-ureter, because obstruction is the most probable cause."

Since the appearance of this paper there have been some important developments in this connection. At that time there were 5 theories as to the etiology of this condition and since then another one has been added and may well prove to be the true explanation.

The five previous theories were as follows:

- 1) That a stricture of the ureter had been present, had been overcome by the progressive ureteral enlargement and had disappeared;
- 2) That a valve had been present and had likewise disappeared;
- 3) That there was achalasia of the ureter; that is, a dys-synchronization between the peristalsis of the ureter and the relaxation of the outlet;
- 4) That there was a neuromuscular disturbance of the ureter; and
- 5) That there was a developmental anomaly in which the ureter retained its early embryological relative size.

The sixth and most recent theory is the result of the work and observations of Svenson of Boston. He showed definitely that the dilatation of the colon in Hirschsprung's disease is brought about by the congenital absence of the ganglion cells of Auerbach's plexus in the terminal portion of the sigmoid causing a lack of peristalsis in that region and, in effect, an obstruction. Complete cures have been obtained by excising the terminal portion of the sigmoid and then re-anastomizing the sigmoid to the rectum. Svenson and his fellow workers had their attention drawn to megalo-ureter by its frequent conjunction with megacolon, and found in cases of megalo-ureter they studied, that there was a marked diminution in the ganglion cells usually found concentrated around each ureteral orifice in the adventitia of the bladder. They suggest that there is, therefore, a mal-developed parasympathetic nerve supply to the bladder, resulting in lack of detrusor power, so that it fills up until the intravesical pressure causes emptying. The treatment they tried was suprapubic drainage for several months, and after that the use of manual compression of the lower abdomen when voiding. This resulted in diminution in size of the ureters and in improved health of the patients. This may well be the solution of the problem of the etiology. Time will tell how permanent the improvement resulting from the recommended treatment will be. It is not a cure—only palliation. And we are still left with the problem of reflux unsolved.

I will now describe three other interesting cases of ureteral dilatation in children.

*Case 4.* Henry Ford Hospital No. 511238. This boy was seen first at the age of 17 with a history of nycturia, frequency and urgency since early childhood. Pus



had been found in the urine on many occasions. He was a sallow, anemic, undernourished boy. The nonprotein nitrogen was 23 mg. per 100 cc blood and his hemoglobin 10.9 gm. per 100 cc blood.

On cystoscopy what was thought to be an opening of a diverticulum was seen on the right. The ureteral orifices were not found and no indigo carmine appeared in 10 minutes. No valves were seen in the posterior urethra, but there seemed to be constriction of the orifice. Cystogram showed what could be interpreted as a partial filling of a voluminous bladder or diverticula and partial filling of a very voluminous right ureter (fig. 4, A). Excretory pyelogram showed nothing.

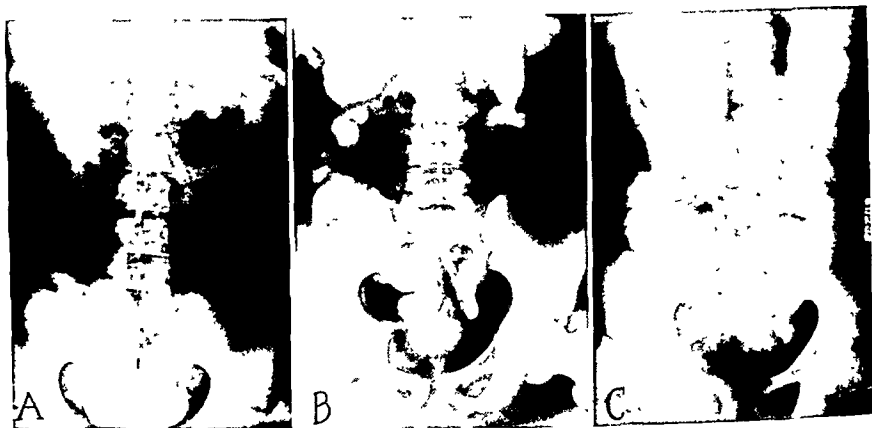


FIG. 4

Suprapubic cystostomy was done and the patient was sent home, to return at intervals to have the tube changed. At the end of 5 months he had gained 40 pounds in weight and looked and felt well. His nonprotein nitrogen was normal and the phenolsulfonphthalein test showed 8 per cent in 1 hour. Cystograms showed huge distended ureters and marked hydronephrosis (fig. 4, B). Transurethral resection of the bladder neck was done, following which he voided freely, with a good stream and the cystostomy promptly closed. However, there was always a large amount of infected residual urine which we thought was largely retained in the huge ureters.

He disappeared from our observation for 22 months and returned following a right sided convulsion. At this time the nonprotein nitrogen was 155;  $\text{CO}_2$ , 12; hemoglobin 9.8; serum chlorides 653; and blood pressure 134/82. He had done satisfactorily at home until 3 months before admission when the urinary stream began to decrease in caliber, he had to strain to urinate and he lost weight.

On admission there was 650 cc clear residual urine. An indwelling catheter was inserted for a few days and his electrolytes returned to normal but the nonprotein nitrogen remained elevated, never falling below 120. Cystogram showed a small bladder but huge ureters (fig. 4, C). He commenced to void a good stream and was sent home. A month later he returned following 2 convulsions and died in uremic acidosis 3 weeks later.

Nothing unexpected was found at autopsy.

This is probably not a case of true megalo-ureter. The primary lesion was probably obstruction at the bladder neck and if it were corrected early in childhood the ureteral dilatation would not have occurred.

*Case 5.* Henry Ford Hospital No. 648641. This is a 4-year old boy who had developed normally. He had had no symptoms, except some urinary dribbling until he had a convulsion 9 months before. Neurological examination at that time showed nothing abnormal. Six months later he had another convulsion. He then was taken to a urologist who made excretory urograms which showed a large and tortuous right ureter with right hydronephrosis. None of the medium was seen on the left side. Following a third convulsion he came to our attention bringing the former x-rays with him.

On cystoscopy, we were able to find both ureteral orifices and made a left ureterogram. The bladder was quite voluminous with a suggestion of hour glass configuration, but there was no evidence of obstruction at the orifice. Urine showed specific gravity of 1.010, a faint trace of albumin, no sugar and no pus. The nonprotein nitrogen was 38 and the hemoglobin 11.8. He had an unusually large head, but a careful neurological examination showed no abnormality.

Operation was done in two stages: first, bilateral nephrostomy and freeing of adhesions between kinks of the upper ureters, which were not greatly dilated; and, second, cystostomy, freeing of lower ureters and excision of 8 inches of the left and 5 inches of the right ureter, thus straightening them. No valve or obstruction was found at either ureteral orifice, nor at the urethral orifice. The bladder was voluminous, slightly thickened and showed fine trabeculation.

Six weeks postoperative the cystostomy wound was healed, there was no urinary frequency, the urine was grossly and microscopically clear; his appetite was good and he was lively and vigorous.

Four months later he had another convulsion and was again admitted to the hospital with a nonprotein nitrogen of 120 but an uninfected urine.

He was discharged a few days later with a nonprotein nitrogen of 42 and urine showing specific gravity of 1.008, a faint trace of albumin and no pus.

Excretory urograms showed no sign of the medium.

He seems well, but has a tremendous thirst.

We have not made cystograms on this boy since operation. In view of the clear urine, we hesitated to chance the introduction of infection.

The prognosis is poor. The operations were apparently useless. This may be another case of megalo-ureter.

*Case 6.* Henry Ford Hospital No. 648674. This was a boy  $2\frac{1}{2}$  years old. His illness began 3 weeks before admission with slight fever. He was admitted acutely ill, with fever and marked pyuria and he was found to have 50 cc residual urine. The nonprotein nitrogen was 22, hemoglobin 8.2. The urine showed specific gravity of 1.010 and there was much albumin and pus.

Cystoscopy showed some trabeculation of the bladder; no gaping of the ureteral orifices which were catheterized with catheter No. 5. The urine from the right showed a few pus cells, that from the left many. Indigo carmine ap-

peared in poor concentration on the right in 7 minutes. It was not done on the left (ureters were catheterized and pyelograms made separately). Cultures showed gram negative bacilli from each kidney and the cystogram showed marked reflux and a large ureter on the left. Pyelograms showed bilateral hydronephrosis and hydro-ureter, more marked on the left. The right ureter showed a bulbous dilatation at the lower end suggesting some obstruction at the orifice, though there was no ureterocele and the catheter entered easily.

Three operations were performed:

1) Bilateral nephrostomy, straightening of the upper ureters and excision of redundant portions. On both sides there was markedly purulent hydronephrosis and hydro-ureter.

2) Excision of a ribbon of tissue from each lower ureter, narrowing and straightening it. On the right the pocket of the ureter below the orifice was also excised. The intramural portions of the ureters were not disturbed.

3) Transurethral resection of a small amount of tissue from the bladder neck.

Two weeks after the resection a cystogram showed reflux on the left, but improvement in the ureter. Suprapubic and cystotomy wounds healed a few weeks after the resection. Three months later his urine cleared and has remained clear. He has gained in weight, seems perfectly healthy and his father says he is full of energy. He has enuresis and occasionally has an accident in the daytime, but this is not infrequent in boys his age. The phenolsulfonphthalein output in February 1922 was 25 per cent in 2 hours.

The evidence in this case points to obstruction as the cause of the condition. The patient has been much improved by the treatment, but whether all the operative procedures were necessary or advisable is questionable and it is doubtful if the improvement will be permanent.

#### CONCLUSIONS

We have reported 6 cases of ureteral dilatation in children, and the operative treatment used in five of them.

Some conclusions seem justified:

1) Reflux up the ureters is not amenable to operative treatment.

2) It seems probable that removal of part of the ureter to remedy tortuosity and kinking resulting from long continued reflux may be useful.

3) Excision of both ends of the ureter with re-establishment of continuity does not result in harm.

4) The work of Svenson and his associates makes it very probable that in the past efforts to remedy or palliate megalo-ureter have been misdirected; that the bladder is the seat of the trouble and not the ureter.

5) Up to date no means of permanently remedying the condition known as megalo-ureter has been devised.

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## PROLAPSING URETEROCELE

LOUIS M. ORR AND JAMES B. GLANTON

Ureterocele, or intravesical cyst of the ureter, is an intravesical ballooning of the distal end of the ureter with involvement of all the component layers of the ureteral wall although the middle coat is usually minimal. This lesion was recognized as such many years ago and probably Lechler in 1835 was the first to describe its characteristics.

Ureterocele is a relatively common lesion to the urologist. It has been estimated that ureterocele will be present in one of each thirty complete genitourinary studies in children. On the other hand, Campbell's autopsy series revealed only one ureterocele in 3,000 cases. This finding can probably be accounted for on the basis that after death the ballooning of the cystic end of the ureter is no longer present and recognition is made difficult. The size of the ureterocele will vary greatly. It may measure less than 1 cm. or may fill the entire bladder. Approximately 15 per cent of all cases of ureterocele are bilateral, with right and left sided involvement being about equal. The lesion has been estimated to be four times as frequent in the female. In one half of these cases there are other co-existent urogenital tract anomalies. In reduplicated upper urinary tracts two-thirds of the cases of ureterocele involve the ureter which drains the upper pelvis.

Several etiological theories have been presented. In support of the congenital origin it may be well, at this time, to review the normal embryological development of the ureter and the kidney.<sup>1</sup> The development of the ureter precedes that of the kidney. The ureteric bud arises from the primary excretory duct. This occurs in the embryo of a total length of 4.5 to 5.3 mm. The absorption of the terminal portion of the primary excretory duct begins in the embryo between 5.3 mm. and 7 mm. greatest length. In embryos of 9.5 mm. greatest length the formation of the funnel is completed and thereby the boundaries between it and the wall of the bladder disappear. The ureters do not grow with equal rapidity. Sometimes the right ureter may enjoy more rapid growth, while other times the left will prove to be the leader. Metanephrogenic tissue, which is developed from the primary excretory duct, accompanies the ureter in its ascent. The various ureteric trees are accordingly covered by metanephrogenic tissue. Each ureteric tree and its metanephrogenic cap form a unit called the primary malpighian pyramid. From these malpighian pyramids eventually develops a kidney. From the complexity of urinary embryology the multiple congenital anomalies that one may observe does not appear to be unusual. Some believe that ureterocele is due to incomplete absorption of Chwalla's membrane with resultant stenosis of the ureteral orifice. Normally this membrane is absorbed in the embryo. This embryological structure is an epithelial downgrowth, or spur membrane formation, which separates the ureters from the primary excretory duct. Others feel that

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 19, 1952.

<sup>1</sup> Keibel, F. and Mall, F. P.: Development of the urinogenital organs. Human Embryology, vol. 2.

ureterocele may be the result of inadequate support of the lower end of the ureteral wall normally supplied by Waldeyer's layer in conjunction with stenosis of the ureteral orifice. Weakness of the submucosal wall is believed by Wilenius<sup>2</sup> to be the most important factor. The lesion is usually considered to be congenital, however, according to some reports it may be secondary to inflammatory changes.<sup>3</sup>

Campbell<sup>4</sup> offers a theory based upon a mechanical equation which seems to be quite rational. He states that, "The renal excretory pressure plus the hydrostatic pressure of the urine, less the relative drainage coefficient of the small metal opening, is in proportion to the amount of dilatation and bulging of the ureterovesical mucous membrane". Campbell's<sup>4</sup> very adequate classification of ureterocele is as follows:

- I. Simple
  - a. Bilateral
  - b. Unilateral
  - c. Reduplication
    1. Reduplication with fusion
    2. Reduplication without fusion
- II. Prolapsed
  - a. External—female
  - b. To prostatic urethra—male
  - c. Vesical diverticulum
- III. Ectopic opening
  - a. Urethra
  - b. Vesical diverticulum
- IV. Blind-ending intravesical cyst

# SYMPTOMATOLOGY

The symptoms of ureterocele are largely those of ureteral obstruction which, if allowed to persist, usually result in hydro-ureteronephrosis. The presence of the ureterocele and its complicating pathological changes are easily demonstrated by a complete urologic survey. Excretory urography will present the so-called classical "cobra head" or "spring onion" filling defect in the lower end of the ureter. Commonly associated complications are most often stasis, infection and calculus formation, with the latter complication occurring in about 4 to 5 per cent of all cases.

# TREATMENT

The main therapeutic objective is to relieve the obstruction with correction of any co-existent congenital urinary tract anomalies. The choice between endoscopic or suprapubic approach may vary with each individual case as both procedures have their obvious merits and indications.

<sup>2</sup> Wilenius, R.: Ureterocele. *Ann. chir. et gynaec. Fenninae*, 39: 78-89, 1950.

<sup>3</sup> Thompson, G. J. and Greene, L. F.: Ureterocele. *J. Urol.*, 47: 800-809, 1942.

<sup>4</sup> Campbell, M.: Ureterocele. *Surg., Gynec. & Obst.*, 93: 705-718, 1951.

TABLE 1. *Reported cases of prolapsing ureterocele*

| NO  | AUTHOR                   | YEAR | AGE                |
|-----|--------------------------|------|--------------------|
| 1.  | Patron                   | 1857 | 14 years           |
| 2.  | Beach                    | 1874 | 5 months           |
| 3.  | Davies-Colley            | 1879 | 1½ years           |
| 4.  | Caille                   | 1888 | 2 weeks            |
| 5.  | Geerdt                   | 1887 | 3 weeks            |
| 6.  | von Hibler               | 1903 | 6 weeks            |
| 7.  | Furnival                 | 1904 | 16 years           |
| 8.  | Geipel and Wollenberg    | 1905 | 13 days            |
| 9.  | Simon                    | 1905 | 52 years           |
| 10. | Hartman                  | 1911 | Not given          |
| 11. | Pietkiewicz              | 1911 | Not given          |
| 12. | Von Franque              | 1913 | Not given          |
| 13. | Santrucck                | 1920 | 33 years           |
| 14. | Kolisko                  | 1921 | Not given          |
| 15. | Nelsen                   | 1921 | Not given          |
| 16. | Pendl                    | 1921 | Not given          |
| 17. | Goertz                   | 1921 | "Une petite fille" |
| 18. | Mayer                    | 1922 | 14 years           |
| 19. | Schroeder                | 1922 | Not given          |
| 20. | Pribram                  | 1925 | 45 years           |
| 21. | Kehrer                   | 1926 | 19 years           |
| 22. | Jeanbrau                 | 1927 | 32 years           |
| 23. | Gilfert                  | 1928 | 20 years           |
| 24. | Davis and Owens          | 1928 | 31 years           |
| 25. | Goldberg                 | 1932 | 47 years           |
| 26. | Hunner                   | 1935 | 21 years           |
| 27. | Hunner                   | 1935 | 34 years           |
| 28. | Rhodes                   | 1936 | 29 years           |
| 29. | Herrick                  | 1936 | 22 years           |
| 30. | Schultze-Rhonhof         | 1938 | 19 years           |
| 31. | H. H. Schnid-Teichenberg | —    | 58 years           |
| 32. | Huth                     | 1939 | 27 years           |
| 33. | Earlam                   | 1940 | 49 years           |
| 34. | Campbell                 | 1941 | 6 years            |
| 35. | Campbell                 | 1941 | 20 months          |
| 36. | Thomas                   | 1942 | 2 years 10 months  |
| 37. | MacPherson               | 1942 | 27 years           |
| 38. | Emmett and Logan         | 1944 | 2 years            |
| 39. | Kickham                  | 1944 | 18 years           |
| 40. | Birdsall and others      | 1944 | Not given          |
| 41. | Abernethy                | 1944 | 41 years           |
| 42. | Hurwitz and McDonough    | 1945 | 10 weeks           |
| 43. | Ortmayer and others      | 1946 | 64 years           |
| 44. | Ingerslev                | 1947 | Not given          |
| 45. | Adams                    | 1949 | 25 years           |
| 46. | Merricks and Herbst      | 1950 | 43 years           |

Prolapse of an ureterocele is not common. Emmett and Logan<sup>5</sup> in 1944 surveyed the literature and collected 37 cases, recording one additional case at the time. Twenty five of the 38 cases occurred in adults and 13 occurred in children less than 15 years of age. In the same year Kickham,<sup>6</sup> and Birdsall,<sup>7</sup> and Abernethy<sup>8</sup> each presented an additional single case, bringing the total to 41. Hurwitz and McDonough<sup>9</sup> in 1945 reported the forty-second case. Ortmayer, Koester and Stetler<sup>10</sup> in 1946 presented the forty-third case, Ingerslev<sup>11</sup> in 1947 and Adams<sup>12</sup> in 1949 presented the forty-fourth and forty-fifth case, and Merricks and Herbst<sup>13</sup> in 1950 presented the forty-sixth case (table 1). All cases reported have been in females. This is not unusual owing to the limitations imposed by the male anatomy. Of the 13 children reviewed and reported by Emmett and Logan,<sup>5</sup> there was a variation in ages between 13 days to 14 years. It is interesting that in this group of children that only 5 of 13 survived operation. The first patient reported to have survived surgery was a girl of 14, who was referred to as a "robust maiden." No doubt she had to be of the Herculean type to survive the surgical ordeal, which consisted of ligation of the sac at the urethral orifice.

Prolapsing ureterocele is, as a rule, easily reducible. Evidence of this fact is gained from the reported experience of a girl 19 years of age. She was by profession a circus performer and was first aware of the prolapse at 14. However, by masterful manual reduction she was able to continue the rather strenuous occupation of equitation for 5 years before submitting to surgical correction. Another patient is reported to have experienced intermittent prolapse of an ureterocele for as long as 20 years.

Ureterocele, if the prolapsing type, in addition to the symptoms and complications associated with simple ureterocele, is further complicated by producing varying degrees of vesical neck obstruction. Gangrenous changes of the prolapsed mass must also be considered. In differentiating prolapsed ureterocele from prolapse of the ureter it is only necessary to observe that in ureterocele there is a definite ballooning out of the smooth mucosal surface, whereas in urethral prolapse there is only an eversion of the mucosa.

#### CASE HISTORY

Insofar as can be determined this is the forty-seventh case of prolapsing ureterocele to be reported.

<sup>5</sup> Emmett, J. L. and Logan, G. B.: Ureterocele with prolapse through the urethra. *J. Urol.*, **51**: 19-23, 1944.

<sup>6</sup> Kickham, C. J. E.: Ureterocele with extension through the urethra. *J. Urol.*, **52**: 235-237, 1944.

<sup>7</sup> Birdsall, J. C. et al: Bilateral ureterocele with prolapse of left ureterocele through the external urinary meatus. *Clinics*, **3**: 58-69, 1944.

<sup>8</sup> Abernethy, D. A.: A case of extension and strangulation of a ureterocele. *Brit. J. Urol.*, **16**: 103-105, 1944.

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<sup>11</sup> Ingerslev, M.: Prolapse of ureterocele as complication of labor. *Nord. Med.*, **33**: 239-240, 1947.

<sup>12</sup> Adams, A. W.: Unusual examples of urethrocele and ureterocele. *Brit. J. Urol.*, **21**: 152-156, 1949.

<sup>13</sup> Merricks, J. W. and Herbst, R. H.: Ureterocele. *J. Urol.*, **64**: 643-645, 1950.



An 11 month old white female (L. B.) was admitted to the hospital, August 24, 1950. The mother stated the child had been well until a few hours previously, when there was observed a reddish mass protruding from the vagina. There had been no previous genito-urinary symptoms. The child was the result of a full term pregnancy, spontaneous delivery, normal birth weight, and no complications. There was one other sibling and no history of congenital anomalies.

On examination the temperature was normal and the general appearance was that of a well developed, well nourished white female in no great distress. The positive physical findings were confined to the vaginal area. There was observed to be an erythematous, moist, glistening, somewhat edematous mass protruding from the vagina, the approximate size of a large walnut (fig. 1). Palpation revealed the mass to be of a cystic character and mild manual compression of this mass produced a spray of urine under considerable pressure. Further examination disclosed that the tumor had prolapsed through the urethra and manual reduction was accomplished without great difficulty. A 20 Foley catheter was left indwell-



FIG. 1. Appearance of vaginal mass on initial examination.

ing. The following day excretory urograms revealed an apparently normal right kidney. On the left was noted only a faint trace of the dye with evidence of pyelectasis and calyectasis. Cystoscopy and retrograde pyelography were carried out under general anesthesia. The cystoscopic picture was that of a large cystic mass occupying the entire left lateral vesical space. The caliber of the tumor remained constant. The ureters were catheterized and an incomplete obstruction was encountered 2 cm. above the left ureteral orifice. Seventy-five cubic centimeters of turbid residual urine was obtained from the left kidney; nothing unusual was noted from the right kidney. The pyelographic findings were consistent with a normal right upper tract, whereas on the left a hydro-ureteronephrosis with a classical "spring onion" defect indicating ureterocele was noted (fig. 2). Following the vertical film the ureterocele again prolapsed through the urethra and the pinpoint ureteral orifice was again catheterized by extra-urethral manipulation. The resultant injected pyelogram revealed a reduplicated ureter with a single common ureteral orifice. Due to the obvious deficient left renal function, the multiple urinary tract anomalies on the left side, and the superimposed infection, a one-stage left ureteronephrectomy was performed through two separate incisions. The bladder and lower ureters were exposed by way of a left lower oblique abdominal incision. Both ureters were clamped, cut, and ligated, including a portion of the bladder. As far as possible all redundant vesical mucosa was retracted

superiorly through the bladder incision at the site of the vesico-ureteral amputation. The amputated ureters were mobilized and the lower abdominal incision was closed in a routine manner. Through a classical renal incision the left kidney



FIG. 2. *A*, retrograde pyelogram displaying normal right upper urinary tract. On left, pyelectasis, calyectasis, ureterectasis, secondary to ureterovesical obstruction. *B*, vertical retrograde pyelogram displaying classical "spring onion" or "cobra head" deformity of ureterocele.



FIG. 3. Left kidney exposed. Note two ureters. Only larger ureter communicates with pelvis. Smaller ureter was found to end blindly but was attached to large renal cyst (note renal cyst is many times larger than renal pelvis).

and attached ureters were removed en masse. An accessory pelvis or renal cyst was observed during the course of the dissection (fig. 3). The postoperative course was uneventful until the next morning during the course of hospital rounds, when much to our chagrin we were confronted by the patient's mother shouting, "The thing is out again." We had realized the possibility of a recurrent prolapse of the

redundant mucous membrane but had neglected to explain this possibility to the parents. A few days later the redundant walls of the ureterocele were excised extra-urethrally and recovery was uneventful.

#### DISCUSSION

The pathological examination of the specimen confirmed the initial diagnosis of prolapsing ureterocele with a resultant hydro-ureteronephrosis above which was a double ureter with a common ureteral orifice. The smaller accessory ureter did not communicate with the renal pelvis but ended blindly at the base of a congenital renal cyst. It is possible that had embryonic development progressed further this congenital cyst would have developed into an accessory renal pelvis with communication with the accessory ureter.

It is of interest that this patient showed no evidence of incontinence of urine following her surgery, although the caliber of the urethra was estimated to be from 40 to 45F at the time of the preoperative examination, which was due to the progressing, continual dilatation produced by the ureterocele.

The patient, up to this time, has remained well.

#### SUMMARY

A case of prolapsing ureterocele is presented in an 11 month old white female. The literature has been reviewed and insofar as can be determined this appears to be the forty-seventh reported case. Surgical correction was instituted in the form of an ureteronephrectomy and extra-urethral excision of the ureterocele. Complete continence of urine has been maintained.

*1300 Kuhl Ave., Orlando, Fla.*

## METASTATIC ADENOCARCINOMA OF THE URETER WITH OBSTRUCTION: CASE REPORT

CHARLES S. MIRABILE AND RICHARD J. SPILLANE

*From the Department of Urology, Hartford Hospital, Hartford, Conn.*

Lymphatic or hematogenous spread of tumor cells to the ureter from a distant, primary source is uncommon. McCrea (1951), in an excellent review of the literature, discovered 39 such cases and reported two additional instances of secondary ureteral involvement. "Implantation" metastases from the renal pelvis and cases of ureteral invasion by direct extension from pelvic or abdominal neoplasms were excluded from the series.

Klinger (1951) studied 5000 autopsies done at the Henry Ford Hospital up to 1948, and found 142 examples of secondary, genito-urinary tract tumors. In the majority of cases (97), multiple portions of the urinary tract were implicated. There were 7 instances of ureteral involvement and in only 1 case was the ureter alone affected.

Porras (1951) reported a single case which was secondary to a breast carcinoma.

The following case is one of metastatic adenocarcinoma of the ureter with obstruction. The primary source proved to be the right lung.

### CASE REPORT

Mr. R. C., a 54 year old, white, sales engineer and private patient of Dr. Rowe A. Castagno, was first admitted to the Hartford Hospital on July 22, 1951 with chills, fever, dyspnea and acute pleuritic pain in the right chest. There was a right pleural effusion with atelectasis. Repeated thoracenteses were done and an average of 350 cc of straw-colored fluid was obtained. The fluid was an exudate; cell blocks were negative for tumor cells, and no tubercle bacilli were found. There was no response to antibiotic therapy and on August 4, a bronchoscopy was done. The findings were not diagnostic and 5 days later an exploratory thoracotomy was performed. Many clots were found in the right pleural cavity with atelectasis. After decortication, the lung expanded satisfactorily.

He was discharged on August 20, but convalescence was slow. Continued chest pain required methadon and he experienced a cough which was productive of mucus with occasional bloody streaking.

On January 16, 1952, he was re-admitted with fever, anorexia, nausea, vomiting, cough, chest pain and weight loss.

Examination revealed a thin, pale, middle aged patient with evident weight loss. The trachea was somewhat deviated to the right. There was a well healed, right thoracotomy scar with minimal excursion of the right chest, dullness on percussion and diminished breath sounds.

Urinalysis on admission was normal and no acid fast bacilli were found on repeated concentration tests. Hemoglobin determination was 12 gm. with a

Accepted for publication July 30, 1952

white blood count of 8,300 cells per cubic centimeter. The nonprotein nitrogen was 42 mg. per cent. Sputum cultures showed the usual mixed flora. The blood sedimentation rate was elevated to 38 millimeters in one hour.

Repeat chest x-rays showed no residual pleural fluid. There was regeneration of the resected sixth rib with united fractures of the fourth and fifth ribs. The mediastinum was retracted slightly to the right. Cholecystogram and examination of the nasal sinuses were normal. The intestinal tract had been thoroughly investigated 3 months previously and the examination was not repeated. An excretory urogram disclosed a normal right kidney with nonfunction of the left kidney.



FIG. 1. Left retrograde pyelogram demonstrates obstruction to Blasucci catheter at 20 cm. Dilatation of middle and lower calyceal structures with incomplete filling of pelvis and remaining renal elements.

On January 29, cystoscopy demonstrated a normal bladder. No indigo carmine appeared from the left ureteral orifice in twenty minutes. There was obstruction to a 5F Blasucci ureteral catheter at 20 cm. and no urine was obtained. Pyelograms were made (fig. 1). The clinical and radiographic impressions were either a chronic, nonspecific, inflammatory process involving the ureter and kidney or renal and ureteral tuberculosis. The patient was prepared with dihydrostreptomycin and on February 5, a left nephro-ureterectomy was done. At surgery, there was a moderate amount of perinephritis with marked thickening of the upper third of the ureter. Microscopic sections showed carcinomatous deposits in the ureter (fig. 2).

The postoperative course was uneventful and he was discharged on February 18. His condition continued to deteriorate with low grade fever, anorexia, chest

pain and weight loss. On May 7, 1952, he was admitted with acute pulmonary edema. The left thorax was enlarged and the right contracted. Respiratory movements were irregular. The heart and mediastinum had shifted to the right. The right lung was dull to percussion with absent breath sounds. Harsh rhonchi and moist rales were present throughout the left lung. A portable chest film showed the right chest to be completely opaque with retraction of the mediastinum and heart to the right. The left lung showed evidence of lymphogenous metastatic spread.

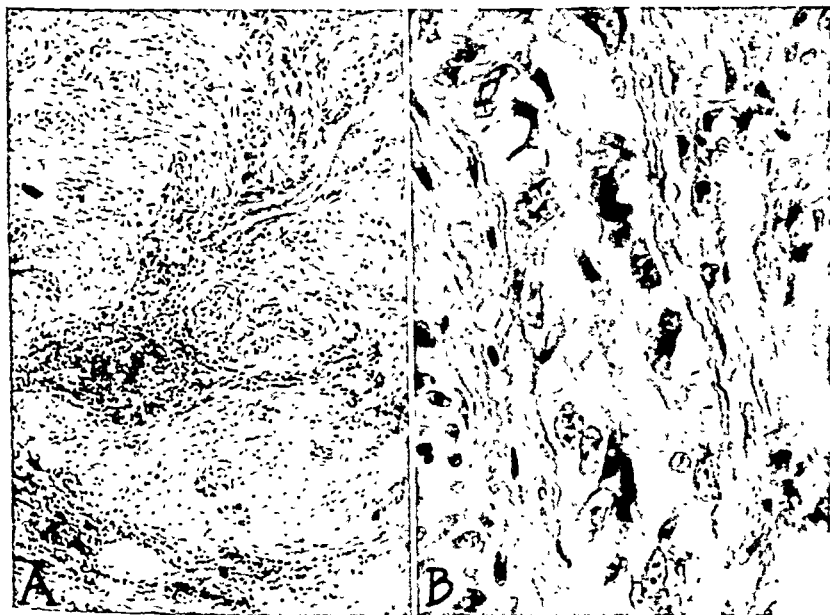


FIG. 2, A, low power photomicrograph shows foci of tumor cells with small nuclei and clear cytoplasm which are somewhat undifferentiated, but arranged in a suggestive glandular pattern. Malignant cells are infiltrating ureter. B, high power photomicrograph to emphasize type of cell encountered.

He died on May 10. Autopsy revealed a bronchiogenic carcinoma of the right lung with lymphatic spread to the left lung. There were metastases to the right kidney, both adrenals and peri-aortic nodes.

#### DISCUSSION

Any level of the ureter may be involved by metastatic tumors. The tunica adventitia is usually invaded first with subsequent spread into the muscular coat and tunica propria by direct extension or along the vascular channels. Ultimately, the mucosa may become attenuated and ulcerated. The nodules may be single or multiple and ureteral obstruction is common. It is frequently impossible to determine by morphologic structure alone whether the lesion is primary or secondary in the ureter and until the primary focus can be identified, there remains a degree of speculation.

In the case under consideration, the right lung was suspected to be the source

of the primary carcinoma; however, it remained for the pathologist to clarify the specific details.

This urological complication is rare, but probably should be included in any differential diagnosis of unexplained ureteral obstruction. The prognosis is extremely poor. Nephro-ureterectomy in the presence of a satisfactory opposite kidney is the treatment of choice. Multiple metastatic lesions of the urinary tract may be anticipated.

#### SUMMARY

A case of metastatic adenocarcinoma of the ureter has been presented and discussed. At autopsy, the primary source was the right lung. The pyelograms were not diagnostic, but indicated ureteral obstruction and hydronephrosis. The roentgen findings were interpreted as representing long standing renal and ureteral tuberculosis or a chronic non-specific infection. The diagnosis was made after examination of the surgical specimen and by postmortem study.

*30 Farmington Ave., Hartford 5, Conn.*

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## PRIMARY CARCINOMA OF THE URETER

WM. NILES WISHARD, JR.

*From the Department of Urology, Methodist Hospital and Indiana University  
School of Medicine, Indianapolis, Ind.*

Primary carcinoma of the ureter, although no longer a medical curiosity, is still sufficiently infrequent to warrant reports of cases as they appear. It is our purpose to report five hitherto unpublished cases, three of which we have seen in the last year or so. Four have been males, one a female. Four have been over 60, one 52. All have had gross painless hematuria whose duration was from 1 day to 2 years. None had metastases as evidenced by physical examination, x-ray, operative findings, or postoperative developments. All the tumors were located in the lower third of the ureter, three on the left and two on the right. Retrograde ureterogram showed fusiform filling defects not less than 3 cms long in 4 instances. The choice of operative procedure must be suited to the patient. If the diagnosis is certain, the lower end of the ureter may be freed, including a cuff of the bladder, by extraperitoneal approach. This gives the advantage of inspection of the ureter. The kidney may be removed at the same time through a lumbar incision.

### CASE REPORTS

*Case 1.* A white, married, male surgeon aet 71 was admitted to the Methodist Hospital May 1, 1950 complaining of gross hematuria in April and May 1949 and March 1950. Urinalysis showed microscopic hematuria. Urologic examination on May 4 showed a little prostatic enlargement, trabeculated bladder, normal left upper urinary tract and obstruction of the right ureter at the juncture of the middle and lower third. On May 8, retrograde injection of the right ureter showed a filling defect at the above point with dilation above of the ureter and pelvis. A diagnosis was made of primary right ureteral tumor with consequent obstruction of the upper tract.

On May 16 the kidney and upper half of the ureter were removed under spinal anesthesia, but the patient's condition precluded prolonging the operation to remove the lower end of the ureter. Pathologic report revealed severe pyelonephritis and moderate hydronephrosis.

On June 12, under spinal and pentothal anesthesia, the remaining portion of the right ureter and its attachment to the bladder were removed through a right pararectus incision. Examination of the ureter showed a fusiform swelling 7 by 2.5 cm. in size at the lower end of the middle third. Upon opening the ureter a soft pinkish gray, exfoliating tumor mass 4.7 by 2.3 by 1 cm. in size was seen. The tumor did not penetrate through the wall of the ureter. Pathologic report was grade 3 papillary carcinoma. No tumor was found elsewhere in the ureter, renal pelvis, or bladder. The patient made an uneventful convalescence from his second operation and was dismissed 10 days later in good condition and reports that he has remained so.

Presidential address read at meeting of North Central Section, American Urological Association, Toledo, Ohio, October 5, 1951.



*Case 2.* A white married male aet 73 entered Methodist Hospital January 13, 1950 complaining of total hematuria of 1 day's duration. His only other complaint was nocturia 1 time. The remainder of his history was irrelevant. Physical examination revealed no abnormality. Plain x-rays and excretory urograms were normal save for prostatic calculi. (The prostate was normal per rectum.) Cystoscopy January 16 (2 per cent metycaine anesthesia in urethra) showed a small collar-like enlargement of the prostate and a bloody efflux on the left. The right urine was normal. The left ureteral catheter was obstructed at 10 cm. and no urine recovered. The right pyelo-ureterogram was normal. The left pyelogram was normal but the ureterogram demonstrated numerous filling defects above the obstructed catheter. The examination was repeated on January 18 under pentothal and the obstruction overcome. A blood tinged specimen of urine was recovered which contained 20 to 30 red blood cells per 4 mm. objective and no other abnormality. Retrograde pyelo-ureterograms showed a normal pelvis and a spindle shaped dilation and nodular filling defects for a distance of 5 cm. at the juncture of the middle and lower third of the ureter. A diagnosis was made of primary carcinoma of the left ureter.

On the day of readmission, the left pyelo-ureterogram was repeated to be sure the filling defects were not clots in the ureter. On February 1, under spinal anesthesia, a catheter was placed in the left ureter and the lower end exposed through a left pararectus incision. A fusiform swelling 5 cm. long was found 10 cm. above the bladder. The ureter was dissected free together with a cuff from the bladder. The bladder opening was closed and the loosened lower half of the ureter dropped back in the incision. The patient was turned on his side and the kidney and ureter removed through a lumbar incision. We elected this sequence in order to examine the lower end of the ureter before taking any irrevocable steps with the kidney. A catheter was placed in the bladder and the patient made a satisfactory recovery and was dismissed February 22.

Upon opening the ureter after its removal a pedunculated tumor 1 by 4 cm. long was found. Its surface was smooth and its base infiltrating the wall of the ureter but not penetrating it. Section of the ureteral tumor revealed an "extensive-neoplastic reaction" arranged over a papillomatous stroma with variation in size and shape of the cells and their nuclei. Final summary: "Papillary carcinoma of the ureter, grade 2." On September 27, 1951 abdominal examination was normal. The patient's general health and nutrition were excellent.

*Case 3.* A white, single, female aet 61 was first seen at our office November 14, 1947 complaining of gross hematuria 2 years previously. On October 6 she had a caruncle removed elsewhere with an increase in her hematuria. She had no pain and no other symptoms. Abdominal examination was not remarkable. Urinalysis revealed 1.25 per cent albumin and many pus cells and red blood cells. Cystoscopy disclosed no evidence of caruncle. Bullous edema was present about each ureteral orifice. A specimen obtained by catheter from the right pelvis showed many red blood cells (traumatic) and no pus. Obstruction was met 7 or 8 cm. above the bladder on the left side and could not be overcome.

On December 2 the patient was admitted to the Methodist Hospital for further

examination. A plain urogram revealed bilateral renal calculi and a probable stone in the lower end of the left ureter. Cystoscopy on December 3 again revealed obstruction in the lower left ureter above which pyelographic media could not pass. Excretory urography on December 4 showed numerous large stones in the right pelvis, which was considerably dilated. The left pelvis was poorly visualized but dilated; shadows of stones were noted in the left pelvis. The left ureter was not visualized. Questionable shadows were observed in its lower third.

On December 6 cystoscopy was again repeated. The left ureter was still obstructed. A wax bulb was scratched. Trauma of the left lower ureter provoked bleeding. Another x-ray showed stones in each kidney but very little calcium density in the shadows in the region of the left lower ureter. The diagnosis at this time was bilateral nephrolithiasis and hydronephrosis with questionable non-opaque stones in the lower left ureter. On December 9 cystoscopy was repeated but the obstruction could not be passed. A wax bulb was negative. Attempted retrograde pyelography showed little dye above the obstruction, the true nature of which was not evident. Ureterectasis and pyelectasis were present.

It was decided to explore the lower end of the left ureter to determine the cause of the obstruction and remove a stone if present. Accordingly on December 12 an electrically lighted catheter was passed up the left ureter 8 cm. where it was obstructed. The patient was taken to surgery and the lower left ureter exposed through an oblique incision above Poupart's ligament. The preoperative diagnosis was left ureterolithiasis (and bilateral nephrolithiasis) with poorly functioning left kidney due to obstructive hydronephrosis.

The ureter above the bladder and below the obstruction was easily identified by the lighted catheter. The lower end of the ureter, including the obstructed portion, was immobilized and in so doing the bladder was inadvertently opened enough to allow the escape of urine. The ureter was considerably larger than normal and firm at the obstructed level. It was opened at the lower point of obstruction and four very small calculi removed. A tongue of polypoid tissue presented itself through this opening, frozen section of which revealed "solid cell carcinoma of the ureter with superimposed chronic inflammatory reaction."

Prior to operation we had not suspected neoplasm, although the fact that trauma from the passage of a catheter provoked bleeding should have made us do so. We were then faced with two abnormal kidneys and a malignancy of the ureter that necessitated removal of one of them. Accordingly, the lower segment of the left ureter, including the tumor was removed, together with a cuff of bladder. The bladder was sutured and a No. 18 urethral catheter passed through the remaining dilated upper end of the ureter to the pelvis, secured by a tie and the wound closed in layers with drainage. Permanent section corroborated the preliminary frozen section. The patient made an uneventful convalescence from this operation.

On December 31 a right pyelolithotomy was done and the wound closed in layers around a nephrostomy tube. On January 28, 1948 the left kidney and upper remaining 16 cm. of ureter were removed through a loin incision. Pathologic report showed one stone 5 by 5 by 3 mm. and severe pyelonephritis and infected hydronephrosis. The patient was dismissed healed on February 11.

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Pathologic report of the kidney showed moderate hydronephrosis with pyelonephritis and arteriolar disease of the kidney. Gross inspection of the ureter showed a fungating soft pink mass 2.7 by 2 by 1.5 cm. in size originating from the ureteral wall in the lower third. The mass was papillary in nature, villous finger-like projections extending from the center. The muscular wall was invaded but not penetrated. Microscopic report: grade 2 papillary carcinoma of the ureter.

The day after operation the patient had hiccough and rapid pulse. Five days later, he was in good condition. He was dismissed on May 18 in good physical and depressed mental condition. His blood pressure was 175/80. The urine still contained pus cells.

In 1940, he had an epithelioma removed from the left side of his neck. On October 25, 1941 he again had gross hematuria. Four days later cystoscopy showed multiple papillary tumors on the floor of the bladder. Two grams of tissue were removed as well as a prostatic bar. Microscopic report was grade 3 papillary carcinoma of the bladder. The slough was scraped off on January 28, 1942 and radon was implanted cystoscopically. On October 27 a necrotic area was still present. This was scraped off on December 15 and some of the radon seeds recovered. Cystoscopy May 13, 1943 showed the bladder was healed. The urine remained clear thereafter. Cystoscopy on June 7, 1945 was negative. Abdominal, rectal and bimanual examination was negative on October 22, 1948. So was the urine. He expired at the age of 79 on January 4, 1950 of coronary disease.

Five instances of primary carcinoma of the ureter have been presented. Symptoms, finding, operative procedure, results and pathology have been discussed. The disease is not too rare, affects males over 60 more than females, and was characterized by painless hematuria in these 5 cases. Ureterography is highly accurate in diagnosis. Nephro-ureterectomy without x-ray therapy is the procedure of choice and is safe.

The first four patients are still alive and well in May 1953.

1711 N. Capitol Ave., Indianapolis 7, Ind.

She has been seen repeatedly since her surgical experiences but has never had any evidence of recurrence of her malignancy.

*Case 4.* A male, white, married, aet 52, entered Methodist Hospital August 4, 1951 giving a history of hematuria of 3 months' duration. It subsided and recurred. The patient had no other significant symptoms. Cystoscopy elsewhere had detected bleeding from the left ureteral orifice.

Cystoscopy on August 6 showed a filling defect in the left ureter at the sacro-iliac level and no other abnormality. This finding corresponded with previous x-rays made elsewhere. An excretory urogram on August 7 showed good function each side and persistent filling defect 4 cm. long at sacro-iliac level of the left ureter. That same day, under pentothal and nitrous oxide, the lower end of the left ureter was exposed through a left pararectus incision and a fusiform swelling 4 cm. long was found at the sacro-iliac level. The ureter was dissected free and severed below together with a cuff of bladder. The bladder incision was closed and the remainder of the incision closed in layers with drainage. The lower end of the ureter was left loose in the incision. A lumbar nephrectomy was then done with removal of a grossly normal kidney and ureter intact.

Examination of the ureter showed no evidence of tumor penetration of the wall of the ureter. Twelve centimeters below the ureteropelvic juncture a tumor 3 by 1.7 by 1.2 cm. in size was found. It was soft and brown. Microsection revealed a grade 4 transitional cell carcinoma with invasion of the epithelium and muscular wall. Examination of the kidney showed chronic pyelonephritis but no hydro-nephrosis.

The patient had an uneventful convalescence and was discharged on August 18 in good condition. He has not been seen since.

*Case 5.* A white, married, aet 66 business man was admitted to the Methodist Hospital March 26, 1937 complaining of hematuria 1 year, 3 months, and 1 week before admission. He had passed clots the size of the lead in a pencil.

Cystoscopy on March 30 showed a normal bladder and right ureteral orifice. The left was red and open and emitted blood. The plain urogram was not remarkable. A right pyelo-ureterogram was normal (double pelvis) and urine from the right kidney contained no pus. The left ureter was obstructed at the level of L<sub>5</sub>. A left pyelo-ureterogram revealed considerable caliectasis, slight pyelectasis, marked ureterectasis down to the midsacroiliac level, and a filling defect for 3.5 cm. below this point. The lower end of the left ureter was slightly dilated.

A provisional diagnosis was made of carcinoma of the left ureter. Because of hypertension and precordial distress, bed rest was instituted for several weeks. Indigo carmine test on April 19 normal on the right, zero on the left. Intermittent hematuria persisted.

On April 27, under ether, a left iliac incision was made and the ureter exposed extraperitoneally. A firm, fusiform swelling 5 cm. long was found at the level of the bifurcation of the iliac artery. The ureter was dissected free, including a cuff of bladder, and the incision closed in layers with drainage. A catheter was anchored in the bladder. The patient was placed on his side and the left kidney and entire ureter removed intact through a lumbar incision.

peated in 3 patients with gross impairment of renal function, the imbalance appeared promptly.

Hypopotassemia has been reported after ureterosigmoidostomy by several investigators, and we have seen 2 cases; it seems unlikely that there is any specific causal relationship between the operation and the hypokalemia, which appears to develop only after prolonged anorexia, vomiting, or diarrhea, despite Korenberg's belief that sodium absorbed from the urine displaces cellular potassium.

#### CLINICAL STUDY

The admission to the hospital of 2 boys who had had ureterosigmoid anastomosis during the first year of life and yet presented dissimilar clinical appearances prompted this report. Four factors have been blamed for the development of hyperchloremic acidosis after this operation: 1) the surface area of the colon exposed to the urine; 2) the frequency and completeness of evacuation of urine;



FIG. 1. A, M. M., urogram on admission B, contrast enema on admission.

3) the segment of the colon bathed by the urine; and 4) the state of the renal function. An attempt has been made by clinical experimentation to evaluate these factors.

M. M., hospital number 776011, aged 4, had an ureterosigmoidostomy at the age of 1 year. Transverse colostomy was done a year later because of persistent chills and fever. He had remained well since that operation, and was admitted for study. He was a normal appearing boy of 4. The excretory urogram (fig. 1, A) showed a normal left kidney and a small right hydronephrosis. Contrast agent injected into the colon revealed a normal colon up to the colostomy without reflux into the ureters (fig. 1, B). The urea nitrogen was 20 mg. per cent, and the plasma bicarbonate and chlorides were 21 and 109 milliequivalents per liter, respectively, a subclinical hyperchloremic acidosis which did not appear to interfere in any way with normal growth and activity.

The second patient, D. B., aged 7, number 736870, had also had an ureterosigmoidostomy at the age of 1, and a transverse colostomy at the age of 2 because of chills and fever. They did not recur but he was readmitted because

## SOME OBSERVATIONS UPON ABSORPTION AFTER URETEROSIGMOIDOSTOMY

C. D. CREEVY

Although Bollman and Mann demonstrated in 1927 that urea could be absorbed from the colon of the dog after ureterosigmoidostomy, and Boyd suggested in 1931 that the presence of acid urine in the colon led to the excretion of fixed base and finally of calcium, widespread interest in the subject is a recent development. Jewett was apparently the first to suggest, in 1940, that the absorption of urinary chlorides from the bowel could produce acidosis in addition to the azotemia from the absorption of urea, and later to show that the former could be corrected by the administration of a low salt diet and alkalis. Ferris and Odel in 1950 found hyperchloremic acidosis in 79 per cent of 141 patients at varying intervals after operation. They confirmed Jewett's observation concerning diet and alkalis, and proved that the condition could also be relieved by means of unilateral nephrostomy or by continuous irrigation of the rectum with tap water. The latter observation demonstrates that the hyperchloremic acidosis is not due to renal disease alone as it is in certain forms of tubular disease. Boyce and Vest, on experimental grounds, surmised that azotemia followed the absorption of urinary ammonia and its conversion in the liver into urea, and that its absorption as the chloride was responsible for the hyperchloremia and the consequent acidosis. Doroshow has suggested that the acidosis may be aggravated by the absorption of organic acids present in the urine or formed by fermentation in the bowel. Renal damage may interfere with the excretion of the phosphates, and with the formation of ammonia by the renal tubules, thus reducing the excretion of the chlorides.

Cordonnier and Lage, and Ferris and Odel have observed that hyperchloremic acidosis may not appear until long after ureterosigmoidostomy, and have suggested that the latent period results from the late development of hydronephrosis and pyelonephritis. Cordonnier and Lage, Doroshow, and Lapidès believe that tubular damage sufficient to impair the excretion of chlorides may result from pyelonephritis too mild to produce a recognizable pyelographic deformity. The observation of Ferris and Odel that unilateral nephrostomy may relieve hyperchloremic acidosis without other treatment emphasizes the importance of the renal factor in its development. Lapidès has demonstrated its significance very ingeniously. Into the rectums of 3 patients whose renal function appeared normal he dripped their own urine while collecting more through an inlying catheter. The urine was expelled from the colon at the end of 3 hours, and that collected in the meantime was then allowed to drip into the bowel. This cycle was continued for as long as 12 days in one patient. The addition of a contrast agent to the urine demonstrated during roentgenography that it reached the cecum. Neither hyperchloremia nor acidosis developed. When the experiment was re-

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 18, 1952.

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Cook, and Lapides together reported upon 106 patients who had excretory urograms 6 months or longer after ureterosigmoidostomy; only twelve or 11.3 per cent had normal appearing kidneys. Since, as already pointed out above, Doroshov, Cordonnier and Lage, and Lapides have suggested that pyelonephritis may damage the renal tubules enough to interfere with the excretion of chlorides without altering the pyelogram, the true incidence of renal disease in the long run is probably even higher than that implied by these figures.

Reflux of urine and feces may also damage the kidneys after transplantation of the ureters into the bowel. Whisenand and Moore saw gas and feces issue from nephrostomy tubes inserted prior to a "mucosa to mucosa" anastomosis and Cordonnier and Lage as well as Parks have commented upon the frequency with which gas is seen in the renal pelves at x-ray after ureterosigmoidostomy. Baker and Miller believe that reflux of fecal material may occur even when normal ureteral orifices are connected to the sigmoid because of the high pressures which normally occur in the distal colon. In view of these unpleasant facts it is surprising that more surgeons have not followed the suggestion of Maucelaire (1895) and Kroenig (1907) that a colostomy be made above the anastomosis to supply a clean reservoir for the urine, uncontaminated by feces. Vest and Boyce have recently reported the urine sterile nine months after such an operation for exstrophy.

#### RENAL DAMAGE AND HYPERCHLOREMIC ACIDOSIS

The records of 111 patients with ureterosigmoidostomy have been studied in an effort to correlate renal damage with hyperchloremia and acidosis. Eighty-one had had the urea nitrogen, chloride, and plasma bicarbonate measured 6 weeks or more after operation. Of the 41 with normal urea nitrogens, there were 44 per cent with hyperchloremia, 22 per cent with acidosis, but only 2.4 per cent with symptoms. Of the forty with elevated urea nitrogens, 75 per cent had hyperchloremia, 70 per cent had acidosis, and 22 per cent had symptoms.

Fifty-three of the 111 patients had urograms 6 weeks or longer after operation. Thirty had at least one normal appearing kidney. Of these, 23.3 per cent had hyperchloremic acidosis, but only 3.3 per cent (1 patient) had symptoms. Of the 23 with bilateral renal disease on urography, 56.5 per cent had hyperchloremic acidosis, and 39 per cent had symptoms, i.e. symptoms were ten times as common in the presence of elevated urea nitrogen or of bilateral renal disease on urography as when the urea nitrogen was normal or when one kidney looked normal. These data can serve only to emphasize the importance of the renal factor in increasing the frequency and severity of hyperchloremic acidosis after ureterosigmoidostomy, even though it is clear that the basic difficulty results from the absorption of urinary chlorides from the colon.

#### THE AREA OF COLONIC MUCOSA EXPOSED TO THE URINE

Case 2 suggests that the area of intestinal mucosa exposed to the urine is not of critical importance in determining the severity of imbalance of electrolytes after ureterosigmoidostomy. A third case confirms this view. L. F., number

of failure to grow, lassitude, and rickets. He had the appearance of a pale, listless boy of 3 or 4. The excretory urogram (fig. 2, *A*) showed poor function, large hydronephroses, and ureters distended down to their entrance into the colon, which was elongated and greatly dilated (fig. 2, *B*). The urea nitrogen was 44 milligrams per cent, and the plasma bicarbonate and chlorides were 9 and 113 milliequivalents per liter, respectively. The hyperchloremic acidosis was corrected and the azotemia reduced by a high fluid intake, the administration of alkalis, and by continuous irrigation of the colon with tap water. Although it was realized that renal damage was dangerously far advanced, the ureters were then reimplanted into the colon at a higher level by Nesbit's method. Drainage of the kidneys was much better (fig. 2, *C*), but the chemistries returned to their former levels shortly after postoperative removal of the rectal tube.

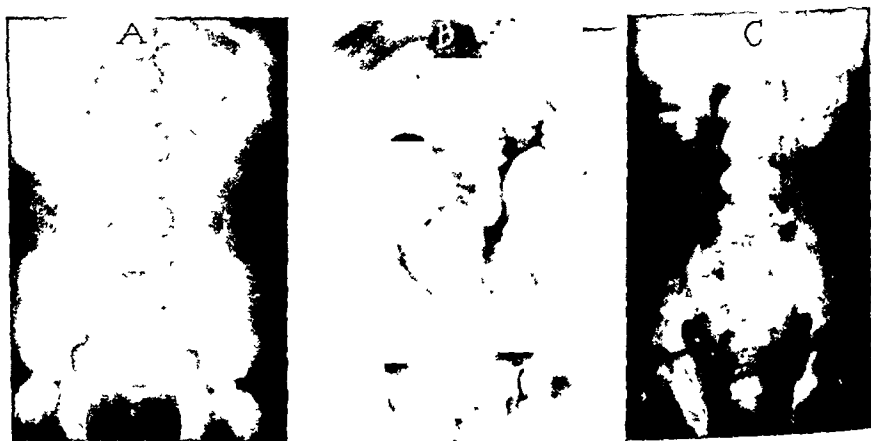


FIG. 2. *A*, *D* *B*, urogram on admission. *B*, contrast enema on admission. *C*, postoperative urogram.

Unaware at that time of the importance of renal damage in producing hyperchloremia and acidosis, and impressed by Boyce's belief that the area of the colon exposed to the urine was important, and by the difference in the colons of the two boys, we excised D. B.'s colon from the colostomy to a point just above the entrance of the left ureter into the bowel. As long as the rectal tube remained in situ, urea and electrolyte balance remained satisfactory, but relapsed promptly upon its removal. A year later the hydronephrosis had diminished and the ureteral stasis had disappeared, but the urea nitrogen was 57 and the plasma bicarbonate and chlorides were 6 and 131 milliequivalents. In other words, the removal of a fairly large area of colonic mucosa had not reduced the imbalance at all, presumably because of irreparable renal damage from hydronephrosis and pyelonephritis.

The frequency with which hydronephrosis and pyelonephritis follow ureterosigmoidostomy is well known. Harvard and Thompson, in a followup study of 198 patients subjected to ureterosigmoidostomy for exstrophy of the bladder, found that there were 52.1 per cent of 20-year survivals; they attributed 67.5 per cent of the late deaths to pyelonephritis. Harvard and Thompson, Pool and

the habit of holding the urine for 5 hours. The urogram (fig. 3) revealed normal appearing kidneys, and contrast agent was seen in the cecum in the 90 minute film. With ideal opportunities for absorption the plasma bicarbonate was 24 (normal) and the chlorides were 111 milliequivalents per liter, a mild elevation, but the renal function was normal.

#### THE SEGMENT OF THE COLON EXPOSED TO THE URINE

Boyce has suggested, on the basis of experiments in the dog, that the segment of the colon bathed by urine is important in determining the degree of absorption, and Merriks has stated that practically no absorption can occur from the cecum because he has observed no hyperchloremia nor acidosis in 12 patients whose ureters had been transplanted into an isolated loop of cecum and ascending colon. I have had no personal experience with this operation but, through the kindness of Drs. Irving Victor and William Mulvaney, have been supplied with data concerning a patient treated by this method in Chicago and observed by them while residents in Urology at the Ancker Hospital in St. Paul. B. S., a man of 75, had the operation described above in April 1950, and was admitted to the Ancker Hospital in November 1950, for intestinal obstruction due to an adhesive band. He recovered after its division and then proved to be in electrolyte balance. In June 1951, he began to have bouts of chills and fever, shortly after which he was found to be in hyperchloremic acidosis. His kidneys excreted no contrast agent, and ureteral catheterization was impossible. The attacks became more frequent and severe and he died in January 1952. Autopsy disclosed destruction of most of the renal substance by hydronephrosis and pyelonephritis. This evidence suggests that enough absorption can occur from the cecum and ascending colon to permit the development of a very severe hyperchloremic acidosis when the kidneys are badly injured.

#### SUMMARY AND CONCLUSIONS

The absorption of urinary chlorides through the mucosa of the colon after ureterosigmoidostomy frequently causes hyperchloremia and acidosis.

Four factors are thought to influence the severity of absorption: the surface area of the colon exposed to the urine; the time of exposure (frequency of evacuation); the segment of the colon with which the urine comes in contact; and the functional capacity of the kidneys.

Clinical experiments with five patients and data concerning a sixth suggest that the last is the most important of these.

Since the kidneys suffer from dilatation and infection more often than not after ureterosigmoidostomy, and since there is no practicable way of preventing the absorption of the urinary chlorides, the solution of the problem appears to lie in protecting the kidneys from infection and obstruction, if this is possible. The most promising method at present seems to involve the making of a terminal colostomy above the anastomoses; much experience will be needed to evaluate the possibilities of this method.

*University Hospital, Minneapolis, Minn.*

750432, aged 38, had severe bilateral hydronephrosis secondary to a contracted bladder filled with papillomas. He was in mild acidosis and uremia on admission, but his plasma chlorides were normal. Because his bladder seemed irreparably damaged ureterosigmoidostomy was done on October 3, 1950 and, in an effort to protect his already badly damaged kidneys, the colon was divided between the descending and sigmoid segments, and the proximal loop was used as a terminal colostomy, thus providing a clean urinary reservoir with a capacity of but 150 cc. Since he proved to be incontinent of urine, the opportunity for absorption was obviously minimal. While the postoperative use of a rectal tube led to normal chemistries, its removal was followed by severe hyperchloremic acidosis ( $\text{CO}_2$  9 and chlorides 135 by January 1951). This seems to prove that the area of colon



FIG. 3. A. G., urogram 2 years after operation. Note contrast agent in secum.

available for absorption is not a vital factor in determining the degree of the imbalance of electrolytes. A fourth case, J. D., number 840276, re-enforces this belief. A mild hyperchloremic acidosis developed 6 weeks after a terminal transverse colostomy and ureterosigmoidostomy (urea nitrogen 27,  $\text{CO}_2$  14, and chlorides 111). Attempted visualization of the colon with contrast agent at this time revealed that the sigmoid was blocked just above the left anastomosis, apparently by kinking. Here again a small loop of colon sufficed to permit measurable absorption, probably aided by a renal deficiency due to mild bilateral hydronephrosis present before operation.

A fifth case presents the other side of this picture. Mrs. A. G., aged 65, number 817015, had ureterosigmoidostomy and cystectomy in March 1950. In February 1952, she had no complaints whatever and had gained 30 pounds. She was in

## CONGENITAL ABSENCE OF URINARY SPHINCTER WITH OPERATIVE CURE

JOHN A. TAYLOR AND WILLIAM H. BERRY

Congenital incontinence is a very distressing condition, which, if not corrected, can lead to social ostracism. It is not a rare condition, when one considers exstrophy with epispadias. However, very few cases of congenital absence of a urinary sphincter in an otherwise normal lower urinary tract have been reported. Campbell<sup>1</sup> does not mention it as a congenital anomaly. Ewert<sup>2</sup> reported a case with operative cure. Hinman<sup>3</sup> states, "Construction of an artificial sphincter is a difficult problem."

Most surgical corrections have been obtained by various methods of angulating the urethra. This angulation acts as a dam to the urinary stream through which the urine is forced by the detrusor action of the bladder. The gynecologists, according to Counseller,<sup>4</sup> have generally attacked this problem with either a Kelly operation, a modified Kelly operation, or a Kennedy operation. All these operations used transvaginal plication of the urethra. The muscle and fascial transplants, which started with Gobel and were subsequently modified by Thompson, Deming, Miller, Aldridge, and others, have the principle of angulating and relaxing the urethra with postural changes. Lowsley and Miller have each used ribbon gut for plication of the urethra. It is evident that the late result in these procedures is a narrowing of the vesical neck by a fibrous ring.

Marshall,<sup>5</sup> in studying incontinence following abdominoperineal resection in 1946, concluded, "Most patients had mobility and marked sagging of the vesical base and outlet, and this suggested the lack of elevation and fixation might be the unrecognized factor". With this principle in mind, he conceived his so-called vesico-urethropexy, in which the posterior urethra and vesical neck and adjoining bladder wall are fixed to the symphysis and recti respectively. This procedure has not been generally accepted, although Marshall reports 19 successes in 25 females with stress incontinence who had not responded to one or more standard gynecological procedures. In a personal communication, he states that he has never had the opportunity to perform it on a case of congenital absence of the urinary sphincter. Doolittle<sup>6</sup> is the only one to report using this procedure. It is a relatively simple procedure, which spelled success in the case herewith presented, after vaginal plication and sling operation had failed. A slight modification was used in our case, in that intact strips of the medial borders of the recti muscle were used in the bladder to rectus sutures because it was rather difficult to approximate the bladder to the strong recti muscles. Since then, this modification

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 20, 1952.

<sup>1</sup> Campbell, M.: *Pediatric Urology*. New York: Macmillan Co., 1937.

<sup>2</sup> Ewert, E. E.: *Lahey Clinic Bull.*, 5: 148-156, 1947.

<sup>3</sup> Hinman, F.: *Principles and Practice of Urology*. Philadelphia: W. B. Saunders Co., 1935.

<sup>4</sup> Counseller, V. S.: *J.A.M.A.*, 146: 1951.

<sup>5</sup> Marshall, V., Pollack, R. S. and Miller, C.: *J. Urol.*, 55: 409-416, 1946.

<sup>6</sup> Doolittle, L. H.: *New Eng. J. Med.*, 246: 366-368, 1952.

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over the catheter until it was quite snug. At the beginning of the procedure, the irrigating fluid dribbled around the catheter. At the conclusion, the urethra was snug enough so that the fluid returned through the catheter instead. The skin over the abdomen was prepared, and a 3-inch incision was made and deepened to the anterior rectus fascia. The fascia and rectus sheath on either side were bared for a width of 1 inch up to the umbilicus. An incision in the fascia was made

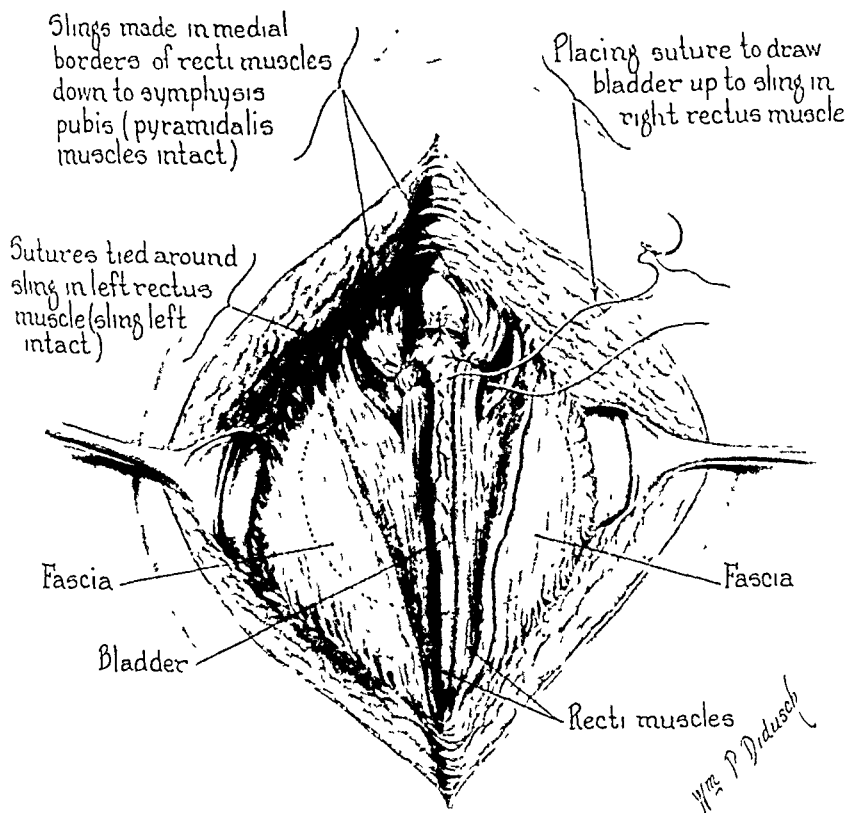


FIG 2

from just below the umbilicus to the symphysis. The fascial slings remained attached at their lower ends. The recti muscles were separated by blunt dissection just posterior to the symphysis. The space of Retzius was entered, and the neck of the bladder and urethra isolated. A clamp was inserted from below on either side of the urethra. The clamp grasped the free end of the fascial slings. The fascial slings were brought out to the vagina on either side of the urethra and brought up retropubically to the opposite rectus, which was pierced, and then the slings were sutured to one another and to the rectus muscle by means of interrupted chromic catgut. The patient was then placed in lithotomy position, and the



has been used in over 20 cases of stress incontinence in women by one of the writers\* who is preparing a report of these cases.

This case is J. L., an 11-year-old white girl, who was admitted to St. Luke's Hospital in June 1949. Her only complaint was complete urinary incontinence since birth. The rest of her history was irrelevant. Examination revealed a normally developed obese female. Vaginal examination revealed a normal vagina,

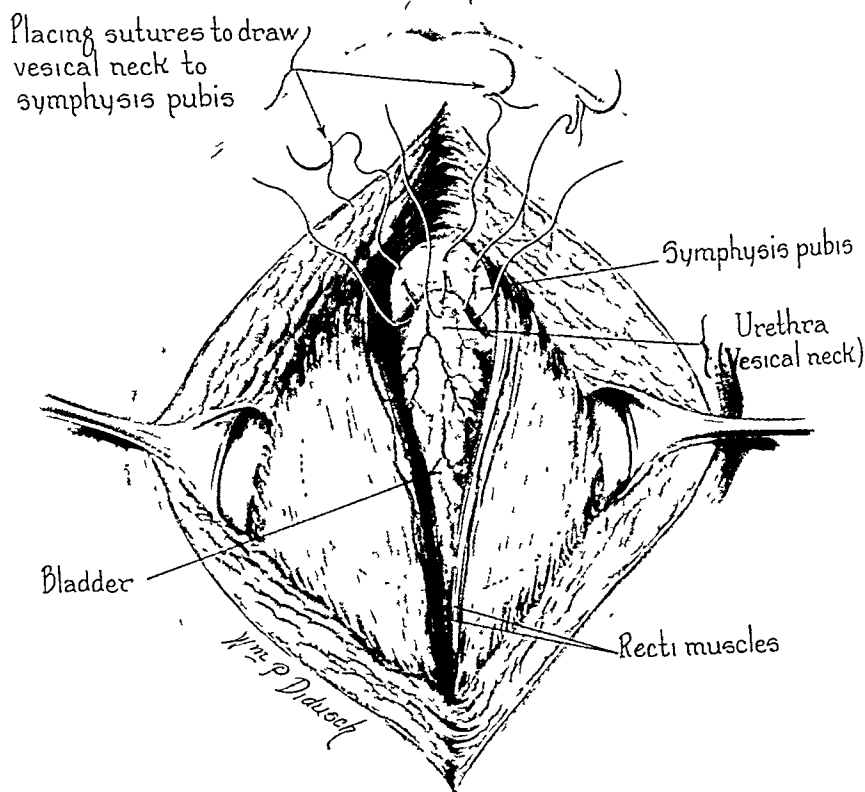


FIG 1

cervix and uterus. There was absence of the left labia, in place of which was the external meatus of a urethra which was patent in its entirety. Cystoscopic examination disclosed nothing abnormal in the urinary tract. The bladder could not be distended because the fluid returned around the cystoscope.

On August 4, under general anesthesia, an incision was made in the vaginal mucous membrane underlying the urethra. Flaps were dissected free on either side, and the urethra plicated with interrupted sutures No. 00 chromic catgut. An 18F Foley bag catheter was inserted into the bladder, and the plication done

\* Dr. W. H. Berry.

## LOCALIZED PANMURAL TUBERCULOUS CYSTITIS: A REPORT OF TWO CASES TREATED BY SUBTOTAL CYSTECTOMY

JAMES C. SARGENT

*From the Department of Urology, U. S. Veterans Hospital, Wood, Wis. and the Marquette University School of Medicine, Milwaukee, Wis.*

Since I have coined the term, I shall define my subject. It refers to an unique and most interesting manifestation of tuberculosis of the urinary bladder having had exceedingly rare reference in all literature.

It is an angry, chronic granuloma, sharply demarcated from adjacent normal or healed bladder structures; is of considerable size and thickness invading all layers of the bladder; and is located in the dome well removed from the bladder base (fig. 1). Quite like the ordinary forms of secondary bladder invasion, it



FIG. 1

apparently occurs as an associated manifestation of renal tuberculosis. Yet unlike the common tuberculous bladder lesions, it is exceedingly refractory to all presently accepted forms of treatment. Indeed it remains obdurate in the face of complete healing of the rest of the bladder following nephrectomy and other appropriate measures of cure.

Something of its unusual character may be judged by the fact that in one of the very few cases described in the literature, Bowen and Bennett<sup>1</sup> at the Peter Bent Brigham reported a fungating, ulcerated lesion the size of a half-dollar situated in the dome of the bladder which was excised under the clinical diagnosis of carcinoma, only to find on section that it was a tuberculoma.

As one browses through the maze of literature dealing with the general subject of genito-urinary tuberculosis, he is struck with the great confusion that prevailed up to and through the first quarter of the century both as it relates to the significance of tuberculous lesions in the bladder and to methods of their treat-

<sup>1</sup>Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 20, 1952.

<sup>1</sup>Bowen, J. A. and Bennett, G. A.: Solitary tuberculoma of the bladder. *Surg., Gynec. & Obst.*, 50: 1015-1017, 1930.

colporrhaphy was completed by means of interrupted sutures. A Foley bag was left indwelling.

The retention catheter was removed on the tenth day, and the patient was able to void two to three ounces of urine with slight incontinence. Her capacity never increased over three ounces, and she still had to wear pads.

Two years later, at the age of 13, she wrote a rather pathetic letter telling about her fear of starting high school with her condition. It was decided to try to do something to strengthen the sling, and so she was re-admitted to St. Luke's Hospital on March 22, 1951. At operation, the suprapubic scar was excised, and the neck of the bladder and the urethra exposed. The slings were located, but they were so imbedded in scar tissue that they had no mobility. Because of the previous vaginal and sling operation on the urethra, the urethra was fixed, and so it was decided that the only hope lay in a vesicopexy. Consequently, three sutures (fig. 1) were placed in the vesical neck, one medial and two laterally, and these were passed through the periosteum of the symphysis, and the bladder neck drawn up to it in this manner. Two bands were split from the recti at their medial borders, and were left intact. Sutures were then passed through the anterior portion of the bladder near the vesical neck, and these were tied around the two intact slings of recti (fig. 2). A Foley bag catheter was left in the bladder. The patient's convalescence was uneventful until the ninth day, when a suprapubic urinary fistula developed. This fistula closed spontaneously and 4 days later the catheter was removed. The patient experienced complete urinary control for the first time in her life, and was able to urinate, although she did have some urgency. She then returned to her home, and follow-up was done by letter. On June 17, 1952, she reports that she is able to hold 8 ounces without wetting herself, but has urgency at this point. She relieves herself at the first inclination of a full bladder, and in this way she is completely continent.

#### CONCLUSIONS

An unusual case of congenital absence of urethra with a surgical cure is presented.

Three main types of operation for incontinence were performed on the same case.

Incontinence continued despite a urethral plication and a retropubic sling operation. Attention is called to the simplicity and efficiency of the vesico-urethropexy.

*2 E. 54th St., New York 22, N. Y.*

Reynard and Michon<sup>7</sup> recounted the details of a case of renal tuberculosis in which a large ulcer persisted in the bladder dome a year after nephrectomy. During the succeeding 6 months curettage of the ulcer, vaginal stretching of the basal nerves of the bladder and laparotomy, with both removal of the thickened ureteral stump and presacral neurectomy, all were done without material change in the fundal ulcer or reversal of the positive culture and bladder symptoms. Finally, almost 2 years after the original nephrectomy the ulcer was excised. Recheck 3 months later disclosed the bladder interior normal save for some limited capacity. Urine cultures were negative and the patient was improved in general health and free of bladder discomfort. The specimen revealed extensive inflammatory changes throughout all layers of the bladder wall with many typical tubercles including giant cells.

It was soon thereafter that Bowen of the Department of Urology and Bennett of the Department of Pathology at Peter Bent Brigham<sup>1</sup> presented their case in most minute detail under the caption "Solitary Tuberculoma of the Bladder." At cystoscopy the lesion was described as a fungating ulcer in the bladder dome the size of a half-dollar, the remainder of the bladder being completely normal. Hematuria and cystitis of some 5 weeks were the symptoms present. Except for several slow-healing scrotal abscesses 10 years before, there was nothing to suggest that the lesion might be tuberculous. Indeed the report does not detail studies of the upper urinary tract either before or after surgery. Excised under the clinical diagnosis of carcinoma, microscopic sections of the specimen revealed widespread inflammation with areas of necrosis, lymphoid, plasma and epithelial cell infiltration and special stains revealed acid-fast bacilli morphologically typical of tubercle bacilli. The bladder wound healed within a few weeks and on discharge the urine was clear, sterile and negative for tubercle bacilli.

#### CASE REPORTS

I should like to report two additional cases in detail.

*Case 1.* Nona, a sickly, half-grown child, was first seen in January 1936, at age 13. An appendectomy had been done 10 years before for intermittent, mild pain in the lower right quadrant referred to the right back. Cystitis had developed at that time and during the intervening years had become increasingly severe despite a variety of medicines.

She was underdeveloped, frail and obviously anemic. The right kidney was both tender and palpable.

The urine was moderately cloudy with much pus and some blood. There were no common staining organisms but acid-fast bacilli were found in abundance.

The bladder examined under anesthesia was violently inflamed throughout and neither orifice could be located.

Excretory urography indicated the left kidney to be anatomically and functionally normal whereas soft tissue calcification and obvious parenchymal cavitation clearly indicated long standing tuberculosis of the right kidney (fig. 2).

<sup>7</sup> Reynard, J. and Michon, L.: Ulcus Vésical Tuberculeux et Cystite Rebelle Cinq Interrémissions Successives. *Journal d'urolog.*, 23: 34-38, 1927.

ment. Particularly confused was the relation, or rather lack of relation, of bladder tuberculosis to pure genital tuberculosis and the literature of those years abounds in false starts at the cure of tuberculous cystitis by epididymectomy or castration, at times even extending to radical removal of the vas deferens and seminal vesicles. That all such treatment was futile so long as reinfection continued from a tuberculous kidney above, finally came to be clearly understood.

The subject of direct treatment to the bladder itself was even more confounded by a variety of methods that were legion. Drug therapy ran the gamut from arsenic orally through tuberculin parenterally to carbolic acid locally. The ulcers were attacked both transurethrally and by suprapubic section using curettage, fulguration and both chemical and thermal cautery. Areas of ulceration were excised. In others the entire vesical lining was denuded. And in still others total cystectomy was employed. Prolonged or permanent drainage was established by cystostomy, by bladder marsupialization and even by the establishment of a vesicovaginal fistula. Denervation through one or another means was recommended. And of course nephrectomy, or when that was forbidden, skin ureterostomy finally came to be standard procedure.

It is little wonder, then, that during the long and interesting period from Paré's time down to and through the early part of the twentieth century one can find very little reference to a sharply localized area of pan-mural bladder tuberculosis sufficiently distinctive in its pathology and behavior to attract special attention. Occasional published references do occur, however, indicating recognition of such a lesion. The first of these that can be found was that of Bryson<sup>2</sup> in 1891. He made the unique observation of what he called a "localized parenchymatous tuberculous cystitis," having observed a sharply circumscribed granulo-matous area the size of a silver dollar on the anterior bladder wall of a male which, after the finding of tubercle bacilli, he decided was a rare type of tuberculous lesion. In 1898, Strauss<sup>3</sup> reported the cure of a case of severe cystitis by excision of an ulcer located on the anterior bladder wall which was tuberculous and considered to be primary within the bladder. Desnos,<sup>4</sup> in 1898, reported briefly on the complete excision of a localized tuberculous bladder lesion and wrote of observing two analogous cases. Louis Schmidt<sup>5</sup> in 1902 wrote in a mere sentence or two of two cases where the bladder was opened and a tuberculous ulcer excised resulting in complete cure. And in 1907, Walker<sup>6</sup> in a most comprehensive discussion of the general subject of bladder tuberculosis based upon 413 cases extracted from the literature and 34 cases on Doctor Halsted's service at Johns Hopkins, noted that among the surgical procedures employed there were 34 suprapubic cystostomies for a variety of procedures and "one excision of the ulcer."

Of such are the scattered and scanty reports on the subject until 1927 when

<sup>2</sup> Bryson, J. P.: Tuberculosis of the bladder. *Internat. Clin. Phila.*, **3**: 162-174, 1891.

<sup>3</sup> Strauss, Von Arthur: Ein Fall von tuberculösem Geschwür der Blase. *Wien. med. Wochenschr.*, **51**: 2403-2404, 1898.

<sup>4</sup> Desnos: Intervention Chirurgicale dans la Tuberculose Vesicale. *Cong. d l'etude de la Tuberculose*. **4**: 864-866, 1898.

<sup>5</sup> Schmidt, L. E.: Tuberculous ulcer of the bladder. *J.A.M.A.*, **39**: 124-128, 1902.

<sup>6</sup> Walker, G.: Tuberculosis of the bladder. *Ann. Surg.*, **45**: 249-283, 388-408, 597-609, 1907.

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<sup>7</sup> Reynard, J. and Michon, L.: *Ulcus Vésical Tuberculeux et Cystite Rebelle Cinq Interruptions Successives*. Journal d'urolog., 23: 34-38, 1927.

No particular attention was given at the time to the sizable filling defect evident in the bladder dome. A chest film showed healed, minimal lung lesions.

The tuberculous right kidney, together with several inches of pipe-stem ureter, were removed. Substantial gradual improvement followed, both in general health and bladder symptoms.

In November 1938, nearly 3 years after nephrectomy, she was found to have gained 17 pounds in weight, felt well generally and her bladder was so greatly improved that she was perfectly happy despite a nocturia of 3 to 4. Her urine, moreover, remained hazy with pus and tubercle bacilli were readily demonstrated.

Excretory urography again indicated the remaining left kidney to be normal



FIG. 2

and the cystogram again gave clear evidence of a sizable filling defect in the bladder vault.

Notes following cystoscopy under anesthesia recorded that "the bladder picture was most remarkable. The mucosa was of normal appearance throughout except for a single, angry, slightly raised and sharply circumscribed ulceration occupying the entire fundus leaving the lower lateral walls, trigone and both ureteral orifices completely healed with but little visible scarring."

The curious sharp localization of the lesion suggested the possibility of cure by radical resection.\* At surgery an area of pronounced induration and thickening the size of a half-dollar was clearly palpable in the bladder fundus. The bladder was mobilized and opened well off to the side of the lesion giving clear view

\* Young's Practice of Urology (1926) vol. I, p. 316 emphasizes the well known hazards of open surgery on the tuberculous bladder.

of the sharply localized granulomatous mass, the remainder of the bladder appearing in all respects completely normal. The lesion was excised with a full centimeter cuff of normal bladder wall.

The pathologist described the gross lesion as being 6 by 8 centimeters in diameter with an average thickness of 18 millimeters and having an enormously thickened, pink, indurated and papillary mucosa with a fibrotic, stringy, leathery-gray cut surface.

Sections revealed the normal muscularis quite completely replaced by chronic inflammatory changes showing numerous tubercles with giant cell inclusions (fig. 3). Recent re-cutting and special staining of the tissue failed to reveal tubercle bacilli.

The cystotomy wound healed readily but reopened in 6 weeks closing permanently after 2 weeks of catheter drainage. During this period of convalescence, daily studies of urine sediment failed to reveal the acid-fast bacilli so easily demonstrated prior to surgery.

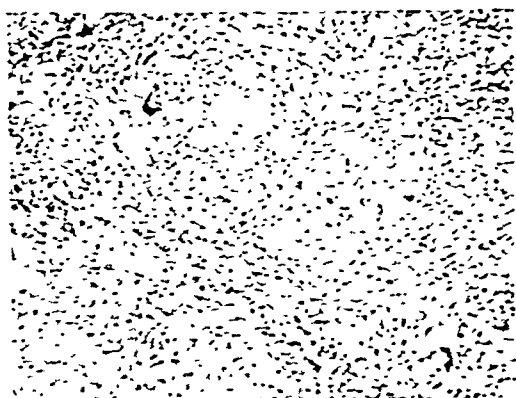


FIG. 3

Clinical recovery was progressive and complete thereafter. In 1941, at age 18 Nona weighed 108 pounds and had a comfortable bladder with nocturia of but 1. The urine was clear; both microscopic and guinea pig tests were negative. Re-examined again 10 years later, as a requirement for the adoption of children, she was a perfect specimen of womanhood weighing 130 pounds, with urine again microscopically and culturally negative.

The second case that I shall present lacks the benefit of definite tissue diagnosis and is somewhat incomplete in detail as to final outcome. There is little question, however, that it, too, is one to be included in this unique category.

*Case 2.* At age 29, E. H. Z. had a left epididymectomy in the spring of 1944 while in military service. That fall cystoscopy was done and pyelograms made because of growing bladder distress and some urinary findings. The patient was given a medical discharge from the service.

In December 1944, he was admitted to the U. S. Veterans Hospital at Wood, Wisconsin for moderate cystitis with pus and blood in the urine. The old hospital



records show that guinea pig tests were positive; that cystoscopy revealed small patchy areas of inflammation in the fundus and posterior bladder wall; and that pyelograms were interpreted as indicating the right kidney normal with calyceal irregularities in the left kidney suggesting tuberculosis. A painful swelling in the right scrotum then led to right orchiectomy and in August he left the hospital against advice. The tissue diagnosis was tuberculous epididymitis.

He was treated by a urologist in another city thereafter and in April 1947, had a left nephro-ureterectomy.

He first came under my care on readmission to the Veterans Hospital in December 1948, a year and a half after nephrectomy. The cystitis had continued moderately severe but the patient's general health was good. Chest films showed



FIG. 4

minimal apical fibrosis. All operative wounds were well healed and the scrotal and rectal findings gave no indication of persisting genital disease. The urine was slightly cloudy with pus and blood. Tubercle bacilli were readily demonstrated on direct smear. Common pyogenic organisms were absent both on smear and culture.

At cystoscopy the bladder capacity was greatly limited and a sharply outlined inflammatory area, covered with a yellowish ragged pseudomembrane, was found involving the bladder fundus and left lateral wall down to and including the left orifice and ridge. The remainder of the bladder appeared quite normal.

The right ureter was not catheterized but the excretory urogram gave no suggestion of right renal disease. An abrupt narrowing of the ureter as it traversed the bladder wall, together with slight stasis above, suggested some ureterovesical cicatrization (fig. 4). The cystogram revealed a notable filling defect in the bladder dome and left lateral wall.

Cultural studies indicated the organism to be sensitive and treatment with a half-gram of streptomycin twice daily, together with 8 to 12 gm. para-aminosalicylic acid was begun and continued for 135 days. No clinical improvement could be noted at the end of 42 days. At cystoscopy, however, the entire bladder was found normal save for sharply limited capacity, slight scarring about the base and a single, sharply-outlined, angry, granulomatous lesion the size of a half-dollar, limited to the left bladder dome. Since acid-fast organisms could no longer be demonstrated by stain of the urine sediment, ureteral catheterization was deemed safe and both the right retrograde pyelogram and ureteral urine cultures indicated the upper right tract to be normal. Streptomycin was continued while awaiting outcome of the cultures and on June 17, when assured of the absence of right renal involvement, subtotal cystectomy was done removing the fundal

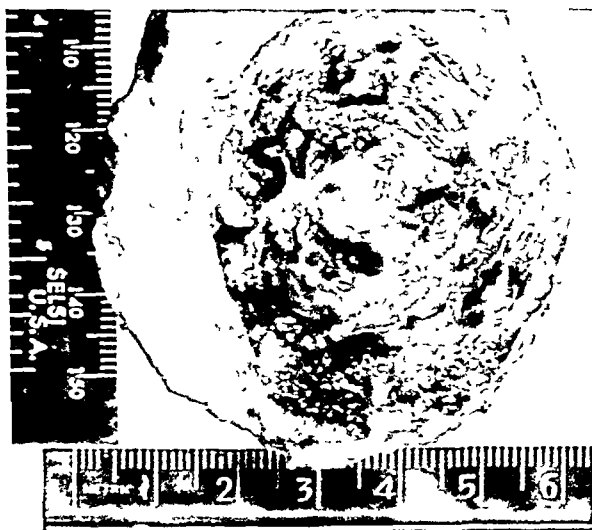


FIG 5

granuloma with a fair cuff of adjacent bladder wall. The balance of the bladder was found completely free of visible inflammatory changes.

The pathologist described the gross specimen as consisting of a portion of the urinary bladder measuring 5 by 5 cm. The mucosa was granular and of a reddish-brown color. The wall measured 12 mm. in thickness and was composed of firm, pale-gray fibrous tissue with mottled reddish-brown areas of softening but without definite tubercles or caseous areas. See figure 5.

Microscopic sections revealed the entire thickness of the bladder wall involved in an extensive inflammatory process most pronounced in the region of the mucosa. In addition to granulation tissue, there were small isolated deposits of calcific material. Definite tubercles could not be recognized and careful search of specially stained sections failed to reveal tubercle bacilli. The pathologist's diagnosis was that of "calcific cystitis."\* See figure 6.

\* Keyes, E. L., Jr. writing on "Treatment of Bladder Tuberculosis after Nephrectomy" in *N. Y. State J. Med.*, vol. 22, p. 553, Dec 1922. discusses postmortem studies of the graver bladder lesions among which "one meets other ulcerations and infiltrations that affect

Immediate postoperative convalescence was normal and the bladder wound closed in due time under catheter drainage. Upon removal of the urethral catheter the patient began with a series of bouts of severe ascending right pyelonephritis which took until November to quiet down with medication and intermittent

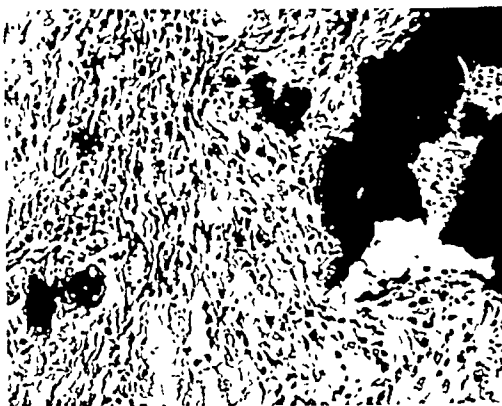


FIG. 6



FIG. 7

bladder catheter drainage. During these several months, a progressive dilatation of the entire upper right side was observed (fig. 7), evidently the result of fibrotic changes in the intramural ureter both causing obstruction and permitting reflux

only limited areas—similar to those of the so-called Hunner ulcer. Sections made from such ulcerations not infrequently fail to reveal any characteristics suggestive of tuberculosis, and it is, therefore, in every way possible that they are predominantly not tuberculous.” Strauss<sup>3</sup> calls attention to the occurrence of phosphatic concretions of tuberculous ulcers.

so that it became obvious that something had to be done to provide better upper tract drainage. In one of his fever-free remissions, he was allowed a short leave and directed to return for either uretero-enterostomy or skin ureterostomy. Cultures on three separate occasions following his bladder surgery had all proven negative for tubercle bacilli though colon bacilli were grown in abundance.

The patient, badly discouraged at the turn of events, promptly transferred for further care to the Wisconsin General Hospital at Madison and I am indebted to its superintendent, Doctor H. M. Coon, for the following details extracted from their records.

He was found on admission there to be well-nourished but appearing chronically ill. His sole complaint was that of terrific cystitis with frequency of 3 to 4 times an hour. There was some blood nitrogen retention. Pyelographic studies revealed substantial hydro-ureteronephrosis due to low ureteral stricture with marked inflammatory changes in all calyces, pelvis and ureter. *B. coli* were grown on plain culture from the right ureteral urine and tubercle bacilli were obtained on delayed special culture. At cystoscopy the bladder was found extremely contracted and distorted with areal cystitis throughout.

On December 7, 1949 permanent right nephrostomy was performed and the patient allowed to go home for Christmas.

A communication from Mr. Z. dated February 14, 1952 indicated that under constant nephrostomy drainage his health had improved considerably and he was working part time as an insurance agent. Despite months of active correspondence I am unable to gain any further information concerning him.

I have hesitated somewhat in reporting this second case because of the lack of clear proof that the excised lesion was in fact a tuberculoma. Is it fair to presume that 135 days of continuous streptomycin therapy cleared the tissue of demonstrable tubercle bacilli and so altered the cellular structure of the lesion as to rob it of its distinctive tuberculous features? Some answer may lie in the fact that long before the course of treatment had terminated the urine had been cleared of culturable tubercle bacilli and the less massive lesions of the remaining bladder mucosa had completely healed. Moreover such a localized massive lesion has no other counterpart in bladder disease and the weight of evidence of associated urinary tract tuberculosis is most impressive.

Doubtless you are left, as am I, with the question as to why such a unique tuberculous lesion; and, particularly, why always in the bladder fundus. Does the answer lie with the two similar questions, still unsolved, concerning simple panmural cystitis?

*324 E. Wisconsin Ave., Milwaukee, Wis.*

## LATE RENAL COMPLICATIONS OF PARAPLEGIA: III: TREATMENT OF VESICO-URETERAL REFLUX BY SKIN URETEROSTOMY THROUGH A PEDICLE FLAP

HERBERT S. TALBOT, DAVID P. PAULL AND GEORGE R. READ

*From the Paraplegia Service and the Urological Section of the Surgical Service, Cushing Veterans Administration Hospital, Framingham, Mass.*

The significance of vesico-ureteral reflux in the development of serious hydronephrosis in paraplegic patients has been noted in a previous report.<sup>1</sup> Further extensive observations have been made on this phenomenon and its associated pathological changes.<sup>2, 3</sup> The natural history of its development, however, its etiology, and its relationship to the pathogenesis of serious renal damage have not yet been thoroughly elucidated.

There can be little doubt that in a large number, perhaps a majority, of instances of damaging hydronephrosis in paraplegics, vesico-ureteral reflux is an early event in the pathogenesis. Whether or not it is the fundamental event is by no means as certain. The significant factor may well be, as Hutch has suggested, an associated functional obstruction at the ureterovesical orifice. Actual organic obstruction is not usually found. Moreover, not all patients with reflux go on to develop renal damage. In many cases, certainly under modern methods of management, the situation remains unchanged for months or years at a time, or shows no further pathological development than moderate dilatation of the ureter or renal pelvis. This applies to bilateral cases as well as those in which it remains unilateral. The reflux may disappear permanently or disappear for a time and then recur. Recent studies by Bors and Comarr suggest that factors as yet incompletely understood may influence the appearance and disappearance of reflux, even during the course of a single examination by combined cystometry and cystography. It is probably unwise, therefore, to accept a single negative cystogram as evidence that it no longer exists.

Because of this uncertain prognosis, because most patients with reflux on one or both sides seem, under close observation, to go on without further difficulty, it has been necessary to limit the concept of operative therapy. To be quite accurate, this report deals not with the treatment of reflux itself, but of certain apparently irreversible changes in the upper urinary tract which sometimes occur in its train.

Before going on to these, a word is in order regarding the management of those patients who have not, or at least not yet, developed these pathological changes. Although reflux cannot be caused by pressure alone, there is little doubt that pressure may exaggerate its consequences; adequate drainage of the bladder is, therefore, essential. This is not an indication for suprapubic cystostomy. In fact, it has been evident from the beginning of these studies that reflux can develop

Accepted for publication July 24, 1952.

<sup>1</sup> Talbot, H. S., and Bunts, R. C.: *J. Urol.*, **61**: 870-880, 1949.

<sup>2</sup> Hutch, J. A.: *J. Urol.*, **68**: 457-467, 1952.

<sup>3</sup> Bors, E. and Comarr, A. E.: *J. Urol.*, **68**: 691-698, 1952.

in the presence of suprapubic drainage. Neither is tidal drainage (with a low siphon loop, of course) categorically excluded, although in most instances its use is probably unwise. A certain number of these patients, if they have well-trained reflex bladders, may continue their regimen of voiding at regular intervals, avoiding over-distension. The elimination of residual urine is an essential safeguard in such cases, as is the maintenance of a relatively uninfected urinary tract. Some may require constant catheter drainage. In every case, the management must be particularized according to the individual needs of the patient and the findings in hand.

In spite of careful treatment, a certain number get into trouble, although only a fraction of those in whom reflux can be demonstrated. The surgical intervention here described is indicated when there are repeated flare-ups of renal infection, or when there is evidence of actual or imminent renal insufficiency. It is apparent, of course, that these will frequently occur in combination; in the later stages this is almost always the case. But, in a given patient, they are likely to present themselves separately, and may conveniently be so considered.

Exacerbations of infection are usually reported by the patient; the history and findings are not remarkable, but, in the absence of other etiologic factors, the recurrent character of the episodes suggests reflux. Demonstrated by cystogram, it may be accompanied by no other structural alterations than, possibly, a minor degree of ureteral dilatation. If the kidney function is good, operation is not immediately indicated. Lavage of the renal pelves may ameliorate the current attack (even when no obstruction can be demonstrated), and a brief course of a suitable antibiotic or chemotherapeutic agent, followed by appropriate management, as already described, may suffice to prevent further flare-ups.

When there is evidence of impaired renal function, or of hydronephrosis of such degree as to make such impairment an early probability, the indication for surgical intervention is more urgent. These cases are more likely to be picked up during routine follow-up examinations than through direct complaint of the patient. The most significant finding is marked bilateral hydronephrosis with hydro-ureter. Azotemia may already be present; this was the case in 2 of the 7 cases here reported. There is almost always impaired or delayed excretion of dye. There is marked delay in the emptying of the renal pelves. Although infection may not be clinically apparent on the occasion of these findings, a history of repeated febrile bouts can usually be obtained. Observations on a considerable number of patients over a period of years, and reviews of the old films of patients seen in a late stage, suggest that with such a picture the pathological changes may be considered irreversible and probably progressive. At this point, in the present state of our knowledge, operative diversion is indicated if the patient is to be saved from further rapid deterioration of his renal function.

In paraplegics, ureterocolic anastomosis is impracticable because of their neurogenic bowel dysfunction. Practically all these patients are incontinent of liquid or semi-liquid stools. Cutaneous diversion is, therefore, the operation of choice. The ordinary flush skin ureterostomy provides satisfactory drainage but is awkward to manage. A suitable coupling device which will maintain a water-

tight seal without irritation of the skin is not available, although the problem has been variously and ingeniously attacked. Freedom from skin complications is particularly important in paraplegics already beset by a tendency to form pressure ulcers. An intubated skin ureterostomy handles drainage adequately but sacrifices the protection from infection which is afforded by a functioning ureter. Fish and Stevenson<sup>4</sup> have described a skin ureterostomy through a pedicle flap which drains well and does not require an indwelling catheter. Their operation, with slight modifications, has therefore been adapted to the cases here discussed. Although the ureter may be considerably dilated, it usually regains sufficient peristaltic function, in time, to provide a good efflux of urine, regardless of the patient's position.

All the patients operated upon have found the management of these ureterostomies easy and convenient. They consider it a change for the better by comparison with a catheter life. They are free from the metabolic complications to which they might be subject after a ureterocolic anastomosis, if such an operation

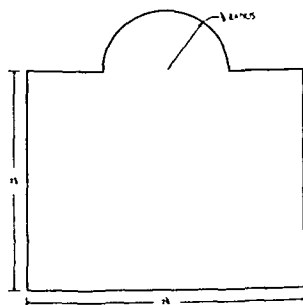


FIG. 1. Pattern used in outlining flap

were feasible. The kidneys remain easily accessible for investigation or treatment through the ureters, should the need arise. It is possible, therefore, that this method of diversion might be applicable in certain patients now being diverted through the lower bowel.

The operation is being performed as a two-stage procedure, the flaps being raised at the first stage and the ureters transplanted at the second. The interval between stages is about three weeks. This permits complete healing of the flaps, and a good development of their blood supply, from which, in turn, the circulation of the distal ureter may later be reinforced. Complete healing facilitates early application of the drainage apparatus. The outline of the pattern for the flaps is shown in figure 1. This is made of sheet aluminum and a tracing made on the skin at the time of operation. The base lies on a line from the umbilicus to the anterior superior spine, with its mid point coinciding with the mid point of that line (fig. 2). The flap is raised from above downward, so that the completed suture line will lie on its superior surface. This avoids a possibility of pressure necrosis when the condom coupling is later applied, since there is likely to be more pressure inferiorly.

<sup>4</sup> Fish, G. W. and Stevenson, T. W.: *J. Urol.*, **61**: 749-752, 1949.

The incision is carried down to the superficial layer of the muscle fascia, and the flap undercut to, but not beyond, its base. Bleeding is controlled by ligation with very fine catgut. The fat on the under side of the flap is trimmed to bring the total thickness to about 0.6 cm. The flap can then be rolled to bring its edges together without tension. Beveling the subcutaneous tissue along these edges will facilitate a neat closure. Care must be taken, however, to avoid compromising the blood supply by removing too much of the flap's substance. The subcutaneous tissue is loosely approximated with 3 or 4 interrupted sutures of fine catgut, the most distal being placed first so that the tip will be straight.

Because of the relative breadth of the base, some tension will be encountered in closing the defect in the abdominal wall. A mattress suture of 0.014 stainless steel wire, placed just above the base of the pedicle, and tied over buttons, will facilitate the repair.



FIG. 2. Outline of flaps traced on skin from pattern

The skin edges of the pedicle are then carefully approximated with fine cotton sutures, the most distal again being placed first. Next, the skin tab is sutured down to form the tip of the pedicle. Use of this tab avoids dog-ears. The subcutaneous tissue of the abdominal wound is closed with interrupted fine catgut sutures, and the skin with cotton. The defect should be closed as it comes together, with no effort to achieve a straight line. The result is usually an elongated "Z". The dressing is applied to support the flap pointing upward and laterally, its most natural position at this stage. The skin sutures are removed on about the ninth and the stay sutures on about the fifteenth postoperative day. Most of the paraplegic patients upon whom this procedure has been performed are anesthetic in the operative area. If sensation remains, a sense of tension may be experienced for a few days. It is of great importance to avoid postoperative abdominal distension, and appropriate measures should be taken to this end.

Beginning on about the fourteenth postoperative day, the flaps should be gradually adapted to their final position, pointing downward and a little mesially. This is accomplished by altering the dressing suitably each day. Edema may develop as a result of circulatory impairment, with some increase in turgor during the early postoperative period, but this always clears up. When it is gone and the



skin has completely healed, the second stage may be undertaken, both ureters being transplanted at the same sitting.

The incision (fig. 3) is made midway between the pedicle and the anterior superior spine on either side. It extends downward from the lower flank in a gentle "S" curve. The ureter is exposed and its lower half dissected from the surrounding structures, leaving as much areolar tissue as possible attached to it. A vessel which usually comes in from the hypogastric artery must be divided in order to obtain a sufficiently long free segment. The ureter is then divided about 2 cm. above its entrance into the bladder and the distal stump closed with a suture ligature of chromic catgut. Two silk ligatures are passed through the proximal cut end, but not tied; they are for use as tractors. The dissection is then developed until there is available a free segment long enough to pass through the pedicle. An accurate measurement is necessary in each case; the average length required is 12 to 14 cm.

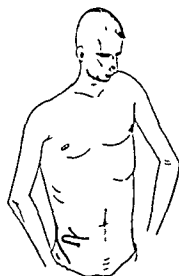


FIG. 3. Location of incision for second stage

A meatus is formed in the tip of the flap by cutting out an elliptical piece of skin about 0.75 by 0.50 cm., avoiding previous suture lines. A bistoury or narrow scalpel is passed through this opening, longitudinally down the center of the pedicle, and through the abdominal wall, remaining extraperitoneal. A straight hemostat is then passed through this tract, and the points spread slightly. The traction sutures on the ureter are grasped and the ureter drawn through the pedicle. Its cut end is then sutured through its full thickness, to the skin edges of the meatus, using No. 120 cotton. There must be sufficient length of ureter to permit this to be done without tension. If a large enough ellipse of skin has been removed, the effect will be an eversion of the ureteral mucosa. Five or six sutures are usually required. If there is tension at this mucocutaneous junction, or if the eversion is not produced, a stricture will almost certainly develop within a short time. Figure 4 is a close-up view of a good meatus, and figure 5, A shows the pedicles after transplantation of the ureters.

A soft rubber catheter (10 to 14F, depending upon the size of the ureter) is passed to the renal pelvis and carefully taped to the pedicle. The wound is closed in layers around a Penrose drain. The patient should be kept well hydrated after operation. The catheters are kept open by irrigation, and the meatal orifices cleaned carefully every day. The sutures are removed on about the ninth post-operative day, and a day later the catheter may be removed and the drainage

apparatus applied. This has already been described.<sup>5</sup> Briefly, a condom, coupled to a tube which leads to a leg urinal, is fixed to the skin of the pedicle with facing cement (fig. 5, *B*). It is changed twice daily and the skin cleansed with soap and water each time. Dried cement is removed by gentle rubbing, with a little cold cream if necessary. Organic solvents may cause dermatitis.

This operation has now been performed on 8 patients, bilaterally on seven, unilaterally on one. Of the bilateral cases, six were paraplegics; the other had long-standing neurogenic vesical dysfunction, associated with an undiagnosed



Fig. 4. Close-up of ureteral meatus showing eversion of mucosa (2 years after operation).

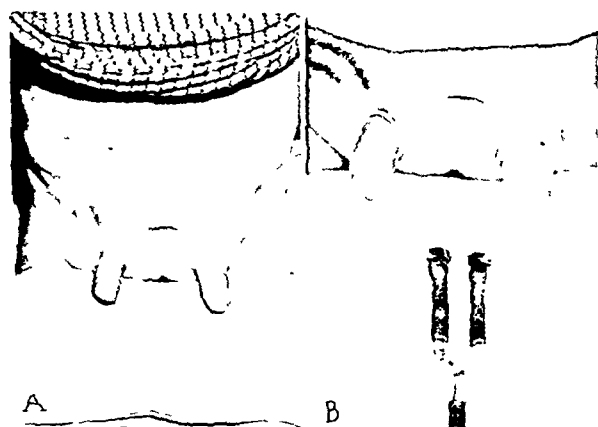


Fig. 5. A, completed pedicles after transplantation of ureters. B, drainage apparatus applied.

spinal cord disease, but no skeletal paralyses. The unilateral operation was done on a patient with carcinoma of the bladder, in whom the function of one kidney had been destroyed by obstruction, while the other showed early hydronephrosis. Following diversion, a total cystectomy was done.

Of the 15 ureters transplanted, there have been complications in four, three of which have been corrected. There were two strictures, both occurring early and probably due to failure to perform the precise technique described. They were successfully treated, with no great difficulty, by revision of the meatus. In 1 patient a tiny fistula developed at the base of the pedicle, where the ureter had apparently been drawn through too close to the skin. This was closed by sealing the ureteral opening with a small skin flap.

<sup>5</sup> Paull, D. P.: *J. Urol.*, 69: 462-464, 1953.

In the one case of unilateral operation a fistula developed from the midpoint of the ureter, closure of which has not yet been attempted. It is probable that in this patient, who is rather obese, there was excessive angulation at the point where the ureter was brought through the abdominal wall. There was also a wound infection which might have been a factor. Pending an attempt at plastic repair, drainage is by intubation and the patient has meanwhile made a good recovery after cystectomy.

All these patients, except for the most recent, whose healing is not yet complete, are doing very well. None has had any further episode of acute renal infection, and the azotemia, which was present in two, has been relieved. The highest nonprotein nitrogen reading is now 42 mg. per cent and this is in a patient whose pre-operative level was 60. The longest follow-up is over 2 years; three other patients have gone over  $1\frac{1}{2}$  years since operation. Roentgenologically, no significant improvement in the hydronephrosis has been noted, but the ureters are less dilated, emptying is better, and renal function is generally improved. All are in excellent health and well satisfied with their present status.

## SPINAL ROOT SECTION IN TREATMENT OF ADVANCED PARAPLEGIC BLADDER

HERBERT BRENDLER, ERICH G. KRUEGER, PHILIP LERMAN, JAMES G. M.  
HARPER, DAVID BRADLEY, MICHAEL H. BERMAN, ARTHUR D. HERTZ-  
BERG, FRED LERMAN and ARCHIE L. DEAN

*From the Paraplegic Service, Veterans Administration Hospital, New York 68, N. Y.*

Following complete transection of the spinal cord, control of micturition by the brain is abolished. Regulation of bladder function is subsequently taken over by a subsidiary center in the sacral cord, which operates through a comparatively simple reflex arc. In the absence of the usual stream of inhibitory impulses from higher centers, the voiding reflex occurs as soon as the intravesical pressure reaches a critical point. This is essentially what happens during infancy and early childhood, before myelinization has taken place.

This sacral reflex mechanism enables a certain number of paraplegics to develop fairly efficient reflex bladders. The majority, however, either never achieve this objective, or else, having achieved it, fail to maintain it. The result in either case is urinary retention. The evolution of the paraplegic bladder merits further explanation.

Spinal cord injury is followed immediately by a variable period of spinal shock, which is characterized by absence of deep reflexes and detrusor atony. During the recovery phase a certain number of bladders regain a measure of function. Micturition in these patients is essentially involuntary, being mediated through the sacral reflex arc, and conditioned solely by the level of intravesical pressure. The voided stream is generally of good force and caliber and is fairly well sustained. The bladder capacity ranges between 200 and 400 cc.; the residual urine is less than 100 cc. Incontinence is rare.

Unfortunately, most paraplegics do not develop reflex bladders. Furthermore, of those who do, a number fail to remain in the reflex state. The bladders in the majority of patients with spinal cord injuries eventually deteriorate into hypertonic, contracted organs. This is a fact not generally appreciated, except at paraplegic centers.

Some of these poor results can be accounted for by mechanical obstruction at the bladder outlet; the value of transurethral resection in these cases is universally recognized. Most failures, however, to maintain an efficient reflex bladder, are probably due to a dysfunction of the sacral reflex arc itself. There is evidence, based on experimental and clinical grounds, that suggests the presence of inhibitory factors within the sacral reflex arc. Lacking help from higher centers, the sacral center may be unable to integrate an effective voiding reflex from the welter of discordant, conflicting stimuli arising in somatic and visceral areas

Read at annual meeting, American Urological Association, Atlantic City, N. J. June 24, 1952.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

below the level of the lesion. Decubitus ulcers, orthopedic conditions, cystitis, bladder calculi and spasms of the lower extremities tend to touch off frequent, premature detrusor contractions. Often the bladder contractions are part of a mass reflex with associated autonomic manifestations, such as headache, sweating and chills. Eventually, the bladder becomes converted into a small, spastic, inefficient organ.

### HISTORICAL RÉSUMÉ

Surgical measures to improve the status of the advanced paraplegic bladder were first developed in connection with the relief of spastic phenomena involving the voluntary muscles. Following the suggestion of Foerster in 1908, posterior rhizotomies were carried out in a number of neurological conditions associated with involuntary spasm.<sup>1</sup> Encouraging results were at first observed in Little's disease, multiple sclerosis and in old injuries of the spinal cord. Later reports, however, were less favorable.<sup>2, 3</sup>

Munro,<sup>4</sup> in 1933, introduced anterior rhizotomy from T<sub>12</sub> to S<sub>1</sub> for the relief of mass spasm after spinal cord injuries. This procedure, designed not to interfere with the innervation of the bladder, found acceptance among a number of neurosurgeons,<sup>5, 6, 7, 8, 9, 10</sup> although there was some difference of opinion regarding the effect of this procedure on the bladder. Munro,<sup>4</sup> Freeman and Heimbürger,<sup>8</sup> Krueger,<sup>9</sup> as well as Kuhn,<sup>10</sup> observed occasional improvement in vesical function. MacDonald, McKenzie and Botterell<sup>6</sup> reported abolition of bladder reflex activity in two cases.

In 1946 Scarff and Pool<sup>11</sup> reported lessening of voluntary muscle spasm following excision of scar tissue from the stumps of the severed cord, and also after surgical section of the dorsal columns caudad to the lesion. These authors suggested the possibility that mass spasm was based on irritation. They did not include observations on bladder function.

For many years it had been known that the bladder was capable of functioning independently of the brain and spinal cord. This type of micturition has been called "automatic" in contrast to the "reflex" variety which occurs in the presence of an intact sacral reflex arc. Goltz and Ewald<sup>12</sup> in 1896, and Müller<sup>13</sup> in 1902, had noted automatic micturition in animals and man following destruction of the

<sup>1</sup> Kuettner, H.: Beitr. klin. Chir., 70: 393, 1910.

<sup>2</sup> Elsberg, C.: Surgical Diseases of the Spinal Cord, Membranes and Nerve Roots. New York: Paul B. Hoeber, Inc., 1941. pp. 123-163.

<sup>3</sup> Freeman, L. W. and Heimbürger, R. F.: J. Neurosurg., 5: 556-561, 1948.

<sup>4</sup> Munro, D.: New Eng. J. Med., 233: 453-461, 1945.

<sup>5</sup> MacDonald, I. B., McKenzie, K. G. and Botterell, E. H.: J. Neurosurg., 3: 421-461, 1945.

<sup>6</sup> Elkins, C. W. and Wegner: Trans. South. Surg. Ass'n., 57: 36-42, 1946.

<sup>7</sup> Kennedy, R. H.: Ann. Surg., 124: 1057, 1946.

<sup>8</sup> Freeman, L. W. and Heimbürger, R. F.: J. Neurosurg., 4: 435-443, 1947.

<sup>9</sup> Krueger, E. G.: Conference on Care of Paraplegics, Washington, D. C. Jan. 15-16, 1948.

<sup>10</sup> Kuhn, R. A.: J. Neurosurg., 6: 320-323, 1949.

<sup>11</sup> Scarff, J. E. and Pool, J. D.: J. Neurosurg., 3: 285-293, 1946.

<sup>12</sup> Goltz, F. and Ewald, J. R.: Pflugers Arch. ges. Physiol. & Pharmacol., 63: 362-400, 1896.

<sup>13</sup> Müller, L. R.: Dtsch. Ztschr. Nervenheilk., 21: 86-155, 1902.

sacral cord. Elliot<sup>14</sup> reported a weak return of bladder automaticity experimentally after surgical division of the pelvic nerves. Denny-Brown and Robertson<sup>15a-b</sup> observed the re-establishment of automatic bladder function without residual urine or incontinence in patients who had sustained a complete injury of the cauda equina. Hoen<sup>16</sup> was the first to carry out anterior rhizotomy of the third sacral roots for the purpose of relaxing the external sphincter. Following this procedure, the patient was able to empty his bladder completely. Browder and Corradini<sup>17</sup> subsequently reported improvement in urinary function after excision of the distal part of the spinal cord in two patients with chronic paraplegia.

In 1948 Sheldon and Bors<sup>18</sup> introduced subarachnoid alcohol block for the treatment of mass reflexes and bladder dysfunction in paraplegia. This method possessed great simplicity as compared with more extensive operative procedures. Our experience with it is described briefly below.

Emmett, Daut and Dunn<sup>19</sup> in 1948 suggested that intradural rhizotomy from L<sub>4</sub> to S<sub>5</sub> be tried in cases where transurethral resection had failed to relieve what they considered an imbalance between detrusor and vesical neck. These authors cited the experiences of Nesbit and Webb, as well as Huggins, Walker and Noonan, who had applied pudendal nerve sections in neurogenic vesical dysfunction, although they considered these experiences as insufficient for a proper evaluation of this procedure. The suggestion of Emmett and coworkers coincided with a report of Heimbürger, Freeman and Wilde,<sup>20</sup> who were able to demonstrate the sacral innervation of hypertonic bladders by novocain blocks and cystometric studies. These authors further pointed out that certain cases of neurogenic bladder, particularly those associated with urinary retention, responded successfully to bilateral injection of the 3rd sacral root with novocain or alcohol. Similar experiences were subsequently reported by Bors, Comarr and Moulton,<sup>21</sup> who evaluated the role of spinal anesthesia, subarachnoid alcohol injections, pudendal nerve anesthesia and vesical neck anesthesia in the management of the traumatic cord bladder.

In 1950, Meirowsky, Scheibert and Hinchey<sup>22</sup> reported their original observations on the bladder status in five cases of spinal cord injury treated by anterior and posterior rhizotomy from T<sub>12</sub> to S<sub>5</sub>, and in three cases after anterior rhizotomy alone from T<sub>12</sub> to S<sub>5</sub>. Satisfactory bladder automaticity developed in six cases. Denervation in the foregoing patients was carried out primarily for relief of incapacitating spasm in the lower extremities. In a simultaneous report,<sup>23</sup> the same authors described a new procedure of differential sacral neurotomy, designed

<sup>14</sup> Elliot, T. R.: *J. Physiol.*, **35**: 367-445, 1907.

<sup>15a</sup> Denny-Brown, D. E.: *New Eng. J. Med.*, **215**: 647-650, 1937.

<sup>15b</sup> Denny-Brown D. E. and Robertson, E. G.: *Brain*, **56**: 397-463, 1933.

<sup>16</sup> Hoen, T. I.: Conference on Spinal Cord Injuries. Army Service Forces, 2nd Service Command, Oct. 20, 1945, pp. 118-119.

<sup>17</sup> Browder, J. and Corradini, E. W.: 17th Ann. Meeting, Harvey Cushing Soc., June 2-4, 1949, New Haven, Conn.

<sup>18</sup> Sheldon, C. H. and Bors, E.: *J. Neurosurg.*, **5**: 385-391, 1948.

<sup>19</sup> Emmett, J. L., Daut, R. V. and Dunn, J. H.: *J. Urol.*, **59**: 439-454, 1948.

<sup>20</sup> Heimbürger, R. F., Freeman, L. W. and Wilde, N. J.: *J. Neurosurg.*, **5**: 154-164, 1948.

<sup>21</sup> Bors, E., Comarr, A. E. and Moulton, S. H.: *J. Urol.*, **63**: 653-666, 1950.

<sup>22</sup> Meirowsky, A. J., Scheibert, C. D. and Hinchey, T. R.: *J. Neurosurg.*, **7**: 33-38, 1950.

<sup>23</sup> Idem. *J. Neurosurg.*, **7**: 39-43, 1950.

specifically to establish bladder automaticity in patients without peripheral spasm. Subsequently, the beneficial effects of this procedure in three patients with incomplete transections of the cord were described by Meirowsky and Scheibert.<sup>24</sup>

#### METHOD OF STUDY

Since 1945 the Paraplegic Service of the Bronx Veterans Administration Hospital has been investigating the applicability of various forms of surgical denervation in the treatment of spastic manifestations involving the bladder and voluntary muscles. In our hands, subarachnoid alcohol blocks have not proved entirely satisfactory. Difficulty has been experienced with precise localization of the block. Also, irritative phenomena have been noted in some cases after alcohol injection.

This paper describes changes in bladder function after surgical section of the sacral nerve roots in twelve complete paraplegics. Eight of these had sustained injuries of the thoracic cord, four of the cervical. In 11 patients bilateral anterior and posterior rhizotomy from T<sub>12</sub> to S<sub>5</sub> was performed in one or more stages. One patient so treated required further division of roots to T<sub>8</sub> because of recurrent spasm of the abdominal muscles. All 11 patients were suffering from incapacitating spasm of the bladder and lower extremities.

Sacral neurotomy from S<sub>1</sub> to S<sub>5</sub> only, as described by Meirowsky et al.,<sup>23</sup> was carried out in 2 patients who were without spasm of the voluntary muscles. In one of these it was done to relieve troublesome bladder spasm, and to encourage the development of bladder automaticity by eliminating the sacral reflex arc. The other was a patient, not included in this series, who was without spasm of any kind, in whom a study was made of the effect of sacral root section on bilateral hydronephrosis and hydro-ureter in the absence of ureteral reflux.

All patients were selected on the basis of preliminary studies of the bladder status either under spinal anesthesia at T<sub>10-12</sub>, or under sacral novocain block<sup>25</sup>. In this manner a state simulating surgical denervation was achieved, thus permitting an evaluation of the feasibility of actual root section. Bladder studies before and immediately after the onset of nerve block included observations of the bladder capacity, voided stream and residual urine. Cystometrograms were obtained before and after block, with the Lewis recording cystometer, using a continuous drip of 15 cc normal saline per minute. Cystograms were made before and after nerve block. Cysto-urethroscopy was done in all patients to investigate the possibility of mechanical obstruction.

As judged from these studies, the indications for denervation were an increase in bladder capacity to at least 250-300 cc, the ability to void voluntarily with only moderate reinforcement by straining or bladder Crede, a residual urine of less than 100 cc, and little or no incontinence.

#### RESULTS

1. *Bladder function.* Postoperatively, in eight of the 12 patients good bladder automaticity developed, as shown by the ability to void satisfactorily and at will.

<sup>24</sup> Meirowsky, A. J. and Scheibert, C. D.: *Exp. Med. and Surg.*, 8: 437-448, 1950.

<sup>25</sup> Meirowsky, A. J., Scheibert, C. D. and Rose, D. K.: *J. Urol.*, 67: 192-196, 1952.

The stream in these patients was of normal force and caliber, although not always well sustained, thereby necessitating some abdominal straining and Credé. Four of the eight no longer required a catheter; in the other four, although the residual urine was not appreciable, constant drainage was required because of ureteral reflux or recurrent pyelonephritis.

Bladder automaticity was only fair in two other patients (one a quadriplegic); a third (also quadriplegic) obtained an equivocal result, and a fourth could not be studied accurately because of poor cooperation. All of these remained on catheter drainage.

Bladder capacity was distinctly increased in ten patients, and ranged from 300 to 400 cc. In the other two, it was unchanged from the preoperative levels (150 and 175 cc), although it had been greater under the influence of novocain block.

None of these patients developed the slightest degree of incontinence, although this has been reported.<sup>22</sup> Cystograms demonstrated that urine was held at the bladder neck in 5 patients, and at the external sphincter in seven. The significance of this is not clear.

2. *Upper urinary tract.* Of 4 patients with serious impairment of renal function, one improved remarkably after rhizotomy. Co-incident with his achieving excellent bladder automaticity, excretion urography demonstrated gratifying improvement, and repeated cystograms disclosed disappearance of bilateral ureteral reflux. Two other patients improved slightly. A fourth, with long-standing renal damage, showed no change.

In all, ureteral reflux was present in 7 patients preoperatively, on one or both sides. After root section, it disappeared completely in four, involved the other side in one originally unilateral, and did not change in two.

3. *General.* After nerve section, 11 patients felt considerably improved generally. One was somewhat better, but still complained of paresthesias in the bladder area and right flank.

Spasm involving the bladder and lower extremities was abolished in all. Upper abdominal spasm subsequently developed in five of eleven patients subjected to anterior and posterior rhizotomy from T<sub>12</sub> to S<sub>5</sub>. In one this symptom became troublesome enough to warrant further root section to T<sub>8</sub>.

Autonomic manifestations, such as headache, sweating, chills and paroxysmal hypertension, were eliminated entirely in all 12 patients.

Although a few patients had experienced random, nonerotic erections prior to rhizotomy, none of the patients had erections postoperatively. Improvement in sexual function has been reported after sacral neurotomy in incomplete paraplegics,<sup>23</sup> but our results do not support this contention. We have observed no change in bowel status after rhizotomy.

#### DISCUSSION

These studies confirm the observations of Meirowsky and his associates that surgical duplication of a transecting lesion of the cauda equina favors the development of bladder automaticity, characterized by voluntary voiding, good bladder capacity, little residual and no incontinence. The clinical significance of this is



immediately apparent. Many paraplegics, hitherto doomed to a catheter existence and its consequent dangers, now may be afforded a chance for urological rehabilitation.

For reasons not yet clear, not all paraplegic patients with contracted, spastic bladders are suitable for this procedure. However, the potential bladder automaticity of candidates for rhizotomy can be ascertained preoperatively in most instances by function studies conducted before and during spinal or sacral anesthesia. In our evaluation, we have relied largely on studies of the bladder capacity, character of the stream and residual urine. The presence of ureteral reflux prevents accurate determination of the bladder capacity and residual urine. Cystography and cysto-urethroscopy have also been helpful. Cystometry, in our hands, has not proved particularly useful, other than providing a graphic representation of pressure gradients. At present, we consider cystometry superfluous for practical purposes.

Section of the anterior roots alone is not as effective as anterior and posterior section in establishing bladder automaticity. This was done in one patient not included in this series, and the bladder remained unchanged. Meirowsky has reported similar findings.<sup>22</sup> It is essential, therefore, that all elements of the sacral reflex arc be completely eliminated. The actual extent of the rhizotomy depends on the degree of associated peripheral spasticity. Section of anterior and posterior roots from  $S_1$  through  $S_5$  appears to suffice for the relief of uncomplicated bladder spasm and for the production of satisfactory automaticity. In some cases differential sacral neurotomy may be enough; this can be determined from the preoperative studies. Quadriplegics have not been significantly improved by rhizotomy. Possibly the loss of abdominal muscle tone and inability to employ Credé pressure on the bladder account for the comparatively poor results in these patients.

Following rhizotomy bladder spasm disappeared in all 12 patients, even in those who failed to obtain a satisfactory degree of automaticity. One wonders whether the resultant bladder relaxation, particularly in the vicinity of the ureteral orifices, was responsible for better drainage from the upper tracts in those patients whose renal function improved postoperatively. Certainly, this is worthy of further investigation because progressive impairment of renal function is the commonest cause of death among paraplegics. Perhaps sacral neurotomy should be done earlier in selected paraplegic patients, to promote better drainage from the ureters, and thus prevent damage to the kidneys which may otherwise become irreparable.

#### SUMMARY

The sacral reflex arc permits the bladder to function reflexly in a limited number of patients after complete transections of the spinal cord. Unfortunately, the majority either never achieve the reflex state, or else deteriorate, so that the end result in most paraplegics is a spastic, contracted bladder.

Surgical section of the anterior and posterior nerve roots from  $S_1$  through  $S_5$ , either alone, or as part of a more extensive rhizotomy from  $T_{12}$  through  $S_5$ , completely abolished incapacitating bladder spasm in all twelve paraplegic patients

so treated. At the same time, this operation facilitated the development of satisfactory bladder automaticity in eight of the twelve.

Patients were selected for operation on the basis of preoperative studies of bladder function conducted under spinal anesthesia or sacral novocain block.

After rhizotomy, renal function improved in three of four patients with serious kidney failure. This may have been due to relief of bladder spasm in the region of the ureteral orifices, thus permitting better drainage from the upper tracts.

We, therefore, suggest that sacral neurotomy be carried out in selected paraplegics before bladder spasm progresses to the point where damage to the kidneys is irreversible.

The authors wish to express their appreciation to Drs. H. K. Faludi, P. A. Price, R. Klebanoff and A. Weiss for their help in this project.

## SACRAL NEUROTOMY FOR THE SPASTIC NEUROGENIC BLADDER

JOHN F. PATTON AND H. G. SCHWARTZ

*From the Sections on Urology and Neurosurgery, Department of Surgery, Washington University School of Medicine and Barnes Hospital, St. Louis, Mo.*

One of the major obstacles to normal social existence in patients with spinal cord injuries is disturbed function of the urinary bladder. Munro has been in the forefront of attack on this problem and has had signal success in developing satisfactory bladder control by early institution of tidal drainage. Either because of known factors beyond control, or for other reasons, suitable bladder function may not be obtained in some patients. It has been noted by Müller and by Denny-Brown that satisfactory automatic bladder activity may occur in subjects with complete destruction of the conus or cauda equina. Freeman and Heimbürger found that capacity of previously hypertonic contracted bladders increased following section of anterior lumbosacral nerve roots, performed for relief of spasticity in paraplegic patients. Chemical interruption of lumbosacral nerves by subarachnoid alcohol injection has been shown by Shelden and Bors to improve bladder function in a high percentage of paraplegics. Meirowsky and his co-workers have demonstrated the possibility of establishing satisfactory bladder automaticity by more limited nerve section. This less extensive operation is particularly suited to individuals with incomplete paraplegia without disabling mass muscle spasm of the lower extremities. Bors has recommended pudendal nerve block or section for restoration of bladder balance. This nerve arises from the second to fourth sacral roots and innervates the striated muscles of the pelvic floor. Limited sacral neurotomy has been effective in the following case.

### CASE REPORT

*J. C. C.* (Hist. No. 180744), a 36 year old white woman, was admitted to Barnes Hospital for the first time on January 29, 1950, because of frequency, urgency, nocturia and incontinence. In 1932, the patient sustained a spinal cord injury secondary to compression fracture of the twelfth thoracic and first lumbar vertebrae. Treatment consisted of immobilization with a body cast. After 3 months of apparently complete motor and sensory paralysis below the waist, there was gradual improvement in motor power. There was an initial 3-week period of inability to void, necessitating catheterization; subsequently there was poor bladder control. The latter has consisted of frequency with low capacity; complete emptying could not be achieved by straining or manual compression. She noted that response to bladder sensation was extremely prompt, resulting in soiling her clothing unless she could reach a toilet immediately. Bowel movements were kept under fairly good control by daily laxatives. The patient was married in 1933. There were no pregnancies. She reported that sexual sensation was deficient, with orgasm during intercourse occurring perhaps once a month. Happy

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 18, 1952.

domestic relations with her intelligent and sympathetic husband were maintained despite the fact that sleep was interrupted by frequency of urination at night (6-15 times).

On admission, the patient was a bright, cheerful young woman. Blood pressure was 148/80. There was moderate kyphosis at the thoraco-lumbar junction. Gait was surprisingly good without requiring support, despite weakness of both lower extremities. There was symmetrical atrophy and weakness of the gastrocnemius, tibialis anticus and extensor hallucis longus muscles. There was contracture of the flexors of the toes, more marked in the left. Knee jerks were active; ankle jerks were absent. Anal sphincter tone was poor. There was hypalgesia from the first to the fifth lumbar dermatomes on both sides, and complete loss of pain sensation below the fifth lumbar dermatome on the right; on the left, there was patchy sparing of pin prick sensation around the vagina, perineum and anus.

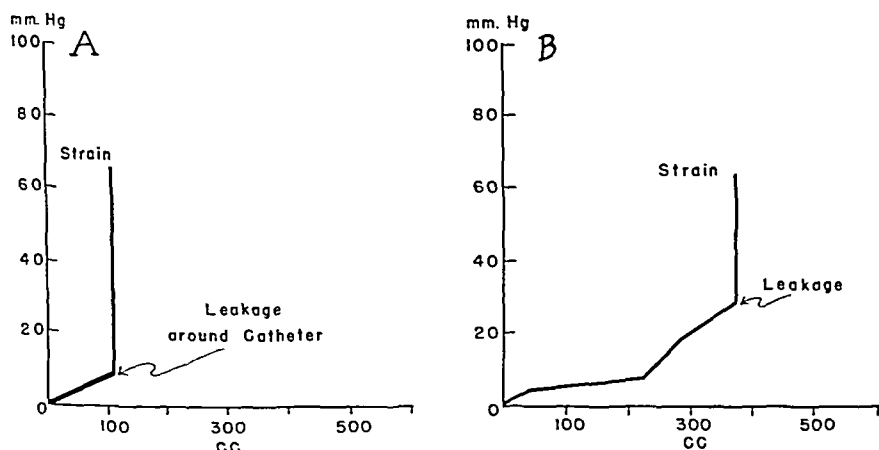


FIG. 1. *A*, cystometrogram showing reduced capacity (110 cc) and hypertonic bladder. *B*, cystometrogram following novocaine block of S2 and S3. Capacity is increased to 375 cc with good voiding pressure.

Touch sensation was diminished below S1. Position and vibratory sense were present.

Bladder capacity was found to be 120 cc, with 70 cc residual. Cystoscopy and cystometry revealed a contracted bladder with marked trabeculation and contracture of the vesical neck. Pyelography revealed a normal upper urinary tract. Transurethral resection of the bladder neck was performed on February 1, 1950. Subsequently the patient voided with less difficulty and improved stream, but continued to have frequency, and voided only small quantities.

Cystometrogram on February 7, 1950 (fig. 1, *A*) showed a capacity of 110 cc and evidence of hypertonicity. Bilateral novocain injection of the second and third sacral nerve roots resulted in increased capacity and good voiding pressure (fig. 1, *B*). Repeated block of these same roots with nupercaine in phenol and benzyl alcohol resulted in improved capacity (600 cc) and marked reduction in frequency over a 24 hour period, following which she reverted to her previous state.

On the basis of temporary improvement after nerve block, operation was performed on February 27, 1950, consisting of bilateral section of the second and third sacral nerves at their individual vertebral foramina. Tidal drainage was maintained for 8 days after neurotomy. The catheter was then removed, and the patient was able to void without difficulty. Figure 2, *A* shows the cystometrogram 15 days postoperatively. She has continued to have good bladder function (fig. 2, *B*), has no nocturia, frequency, or urgency. Motor power of the lower extremities has not been affected, nor is there any objective sensory change. The patient reports increased sexual gratification with orgasms occurring more frequently. In June 1951, her menstrual period was protracted and she complained of headache and shortness of breath. She was found to have hypertension (210/130) and was re-admitted to the medical service for study. During the course

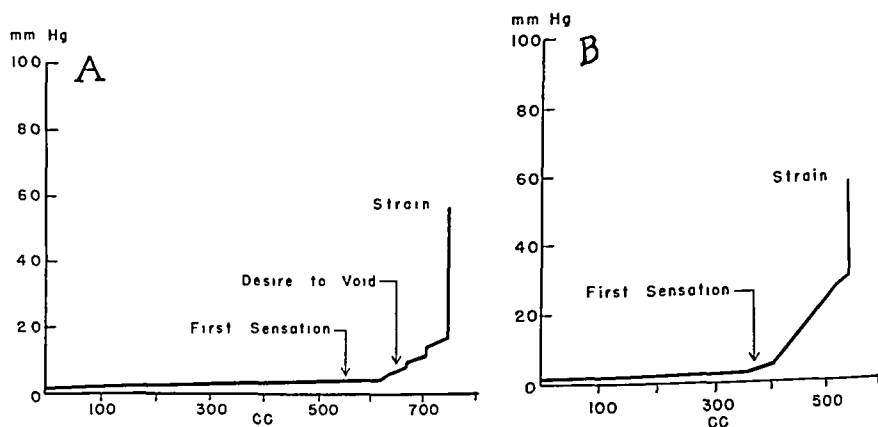


FIG. 2. *A*, cystometrogram 15 days after bilateral sacral neurotomy, S2 and S3. Patient voided 200–750 cc with capacity over 800 cc. No incontinence. Residual 5 cc. *B*, cystometrogram 16 months after sacral neurotomy. Patient voids 4 to 5 times a day, goes 10 hours at night and no incontinence.

of this hospitalization, cystometrogram was found to be essentially normal (fig. 2, *B*). Cystoscopy revealed only mild trabeculation, and the upper urinary tract was found normal by pyelography and differential function.

#### DISCUSSION

There has been some confusion in terminology concerning the presence of a "reflex" and "automatic" bladder. In many instances the terms are used interchangeably. It is desirable to limit the term "reflex bladder" to those cases where bladder function depends upon the integrity of a segmental reflex arc in the lower part of the spinal cord or conus. This type of vesical function is the most frequently encountered in patients with cord injury, and presents the group in which Munro has effectively taken advantage of reflex activity to produce a satisfactory bladder.

"Automatic" bladder function occurs in cauda equina lesions, where innervation by way of segmental spinal connections is interrupted. Clinical observation,

cystometric study, and cystoscopy suggest that relaxation of the vesical wall, bladder neck and perineal muscles follows limited sacral neurotomy just as it does after complete lumbosacral rhizotomy. Since the bladder neck is believed to receive a significant portion of its nerve supply by way of the lumbar nerves, an explanation for relaxation of the neck following a procedure which does not interrupt the lumbar nerves must be sought. It is conceivable that opening of the bladder neck is facilitated by relaxation of the pelvic floor. An alternative, and perhaps more acceptable physiologic explanation may lie in the fact that afferent impulses from spastic perineal muscles enter the cord through sacral roots and reach the internuncial pool of the bladder center in the lower spinal cord, where they play upon the efferent fibres which go out through the lumbar nerves to the bladder neck. Reduction of afferent impulses after release of spasticity in the perineal muscles would reduce the effect in the internuncial pool and cut down on the intensity of efferent stimuli reaching the bladder neck. The validity of such a mechanism might be tested by differential sacral posterior root section.

#### SUMMARY AND CONCLUSIONS

A case is presented in which a spastic bladder secondary to spinal cord injury was converted into a satisfactorily functioning organ following limited bilateral sacral neurotomy.

A distinction is made between "reflex" bladder and "automatic" bladder. The mechanisms by which relaxation of the bladder neck occurs after section of the sacral nerves is discussed. A theory is presented with postulates that fewer stimuli reach the bladder neck from the internuncial pool of the lower spinal cord because of afferent impulses from spastic perineal musculature.

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## EVALUATION OF SIZE OF BLADDER NEOPLASMS

C. D. BRUNKOW

The necessity for the urological surgeon to know accurately the dimensions and location of bladder neoplasms, excepting small papillomas, is most important in helping to decide just what plan of procedure is to be used: whether to resect the growth transurethraally by one or more sittings and possibly implant radon seeds, or just to open the bladder and fulgurate thoroughly or do a segmental resection.

No matter how proficient or expert one becomes in cystoscopy, the visual interpretation in medium or large sized growths is, in a larger percentage of cases, inaccurate, as proven when the bladder is opened and directly under the eye.

Excretory urograms should always be made in cases of tumor at the base of the bladder on the lateral walls to determine possible infiltration of the ureter with a nonfunctioning kidney above.

By a simple, painless method, without complications, it is possible to obtain far more information about these neoplasms before operation and thus become more precise about the procedure that one is going to use (fig. 1).

It is impossible many times to attempt to evaluate large tumors even with the patient under spinal anesthesia.

For a long time, cystograms with sodium iodide were done in cases of bladder tumor; the only information obtained was the apparent filling defect, shown by a flat x-ray film, and on many occasions they were at variance with the true condition as seen at time of operation.

To eliminate these visual errors and learn more in detail about bladder neoplasms, we suggest the use of a thorium preparation called Umbrathor, and the taking of a supine and lateral cystogram. Umbrathor adheres to a tumor or foreign body in the bladder and cannot be washed off.

It requires only a few minutes of time and the procedure is as follows:

A 22 or 24F catheter is inserted through the urethra and a notation made whether the urine contains blood clots. If this is the case, it is necessary to remove the clots because of the inaccuracy which might result from their presence.

The cystogram is accomplished by injecting 1 to 1½ ounces of the thorium solution into the bladder. After 3 minutes, by actual timing, the bladder is filled to capacity with water. The catheter is then clamped.

The first exposure is taken in a supine position; this is followed by a second exposure in an oblique position, the pelvis being at an angle of 45 degrees with the table.

These two exposures give the appearance of an opaque consistency similar to those when sodium iodide is used in the method that is familiar to all urologists.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 20, 1952.

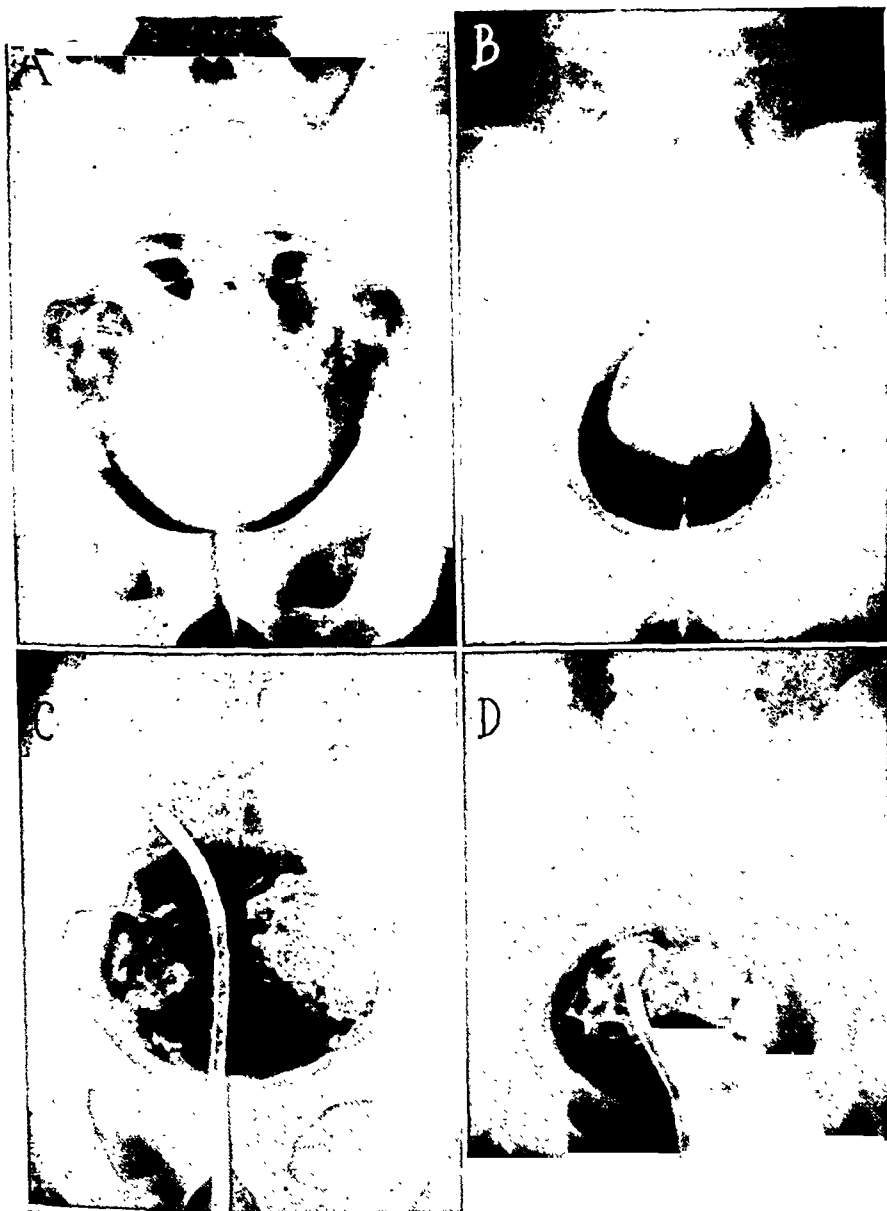


FIG. 1. *A*, opaque cystogram made with Umbrathor solution. *B*, pneumocystogram made after several irrigations and replacement of bladder with air; note tumor at dome of bladder. *C*, pneumocystogram; note tumor on both lateral walls and several at base of bladder. *D*, pneumocystogram; note multiple non-opaque calculi.

The bladder is then emptied using several irrigations until the fluid is relatively clear. This should remove all the thorium solution excepting that which adheres to the tumor mass.

Air is then injected into the bladder in the same volume as fluid was used in



the opaque cystograms. This gives a contrasting pneumocystogram with the maximum amount of information preoperatively.

The true bladder capacity will be represented in black and those areas that show the Umbrathor clinging to them are bladder lesions of one kind or another, and are true in all their dimensions and location. The oblique exposure in some cases reveals invasion of the neoplasm in the posterior or lower portions of the bladder, these are not visualized in the anterior-posterior positions.

*31 Lincoln Park, Newark 2, N. J.*

## CONSERVATIVE SURGERY IN THE TREATMENT OF LARGE SINGLE PAPILLARY TUMORS OF THE BLADDER

DANIEL R. HIGBEE

We live in an era in which radical surgery is becoming both commonly practiced and popular. This attitude naturally extends to the treatment of carcinoma of the bladder.

For the older members of our specialty who have attained their perspective through wide experience in dealing with all forms of bladder malignancy, the proper selection of an operation to be employed is no great problem.

However, for the younger man who is forced to substitute precept for experience, the selection of the proper method of dealing with various types of bladder tumors is not so easy, and I am mindful of his problem in presenting the following group of cases which have been deemed suitable for conservative surgery.

TABLE 1. *Bladder tumors. 131 cases; 1933-1950*

|                                            | MORTALITY |                    |
|--------------------------------------------|-----------|--------------------|
|                                            | No. Dead  | Percentage         |
| 36—Single papillomas                       |           |                    |
| Rx. Transurethral fulguration              | 0         | 0                  |
| 82—Papillary transitional cell carcinomas  |           |                    |
| 46 Transurethral fulguration               | 4         | 9%                 |
| 11 Palliative treatment                    | 11        | 100%               |
| 8 Suprapubic fulguration                   | 2         | 25%                |
| 6 Suprapubic resection                     |           |                    |
| 8 Segmental resection                      | 2         | 14%                |
| Nephrectomy—ureteral transplant            |           |                    |
| 3 Total cystectomy                         | 2         | 66 $\frac{2}{3}$ % |
| 13—Squamous cell or infiltrative carcinoma | 11        | 83%                |
| 6—Total cystectomy                         | 5         | 83 $\frac{1}{3}$ % |

The factual material for this presentation has been drawn from 131 cases of tumors of the bladder treated between 1933 and 1950 inclusive and is presented for the purpose of background only (table 1).

Of this number, 36 were single papillomas treated by transurethral fulguration without subsequent recurrence and with no mortality related to the bladder tumors.

Eighty-two tumors were classified by the pathologist as papillary transitional cell carcinomas. Of these single and multiple tumors, 46 received either single or repeated transurethral fulgurations, 4 dying eventually of recurrences.

Of the remaining 35 cases, eleven were inoperable and received palliative treatment in the form of suprapubic drainage, bilateral nephrostomy or ureteral implantation into the bowel.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 18, 1952.

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Eight were treated by open suprapubic fulguration. Of this group six are alive and well and two are dead of bladder malignancy following recurrences and other procedures.

Six were treated by segmental resection of a full thickness of the bladder, the tumors lying in an area which did not involve a ureter. Of these, five are alive, one is dead following later cystectomy for recurrences.

Eight were treated by segmental resection with either nephrectomy or bladder re-implantation of the affected ureter. In this group there was one postoperative mortality from a pulmonary embolus and one is dead five years postoperatively without a recurrence. The remaining 5 are alive and well from 1 to 17 years. Of 3 total cystectomies, one is alive and apparently well 2 years postoperatively.

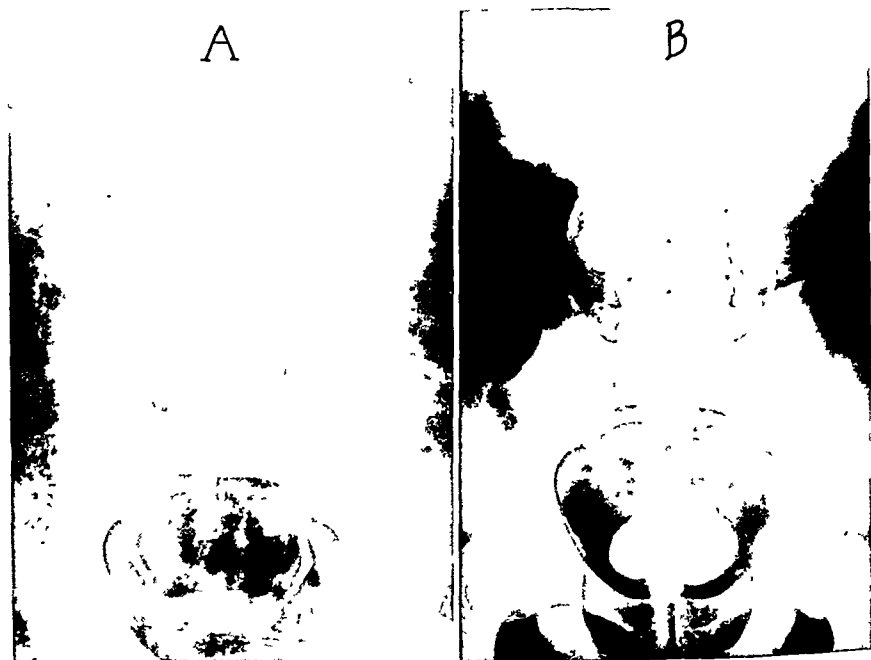


FIG. 1. Before and after segmental removal of papillary carcinoma of bladder. Hematuria, 4 months. Tumor size: 2 by 2 by 1 cm. Grade 2, base invaded 0.1 cm, fairly wide. Well, 9 years; no recurrences.

Thirteen tumors were classified as either squamous cell or solid infiltrative tumors; of this group, two are alive, one, 11½ years postoperatively and one, 4½ years postoperatively.

The group of tumors which I wish to discuss in some detail is the large single papillary tumor of the bladder treated either by segmental resection alone, or by segmental resection with nephrectomy or re-implantation of the ureter of the affected side.

Five of the 6 patients comprising the first group had noticed hematuria varying from 1 week to 1 year's time. One patient presented himself with a chief complaint of acute urinary retention without a history of hematuria. Two tumors in this group were biopsied by examination of tumor particles obtained with the

evacuation of clots from the bladder, 22 gm. tumor tissue being obtained in 1 case.

The tumors, as shown in the accompanying slides (figs. 1, 2, 3), were comparatively large, measuring on the average 3 to 5 cm. in greatest diameter and from 1 to 1.5 cm. through the pedicle.

In this group recurrences developed in 2 cases and have been controlled by subsequent transurethral fulguration, 1 twice and the other four times. Neither patient is suitable physically for total cystectomy.

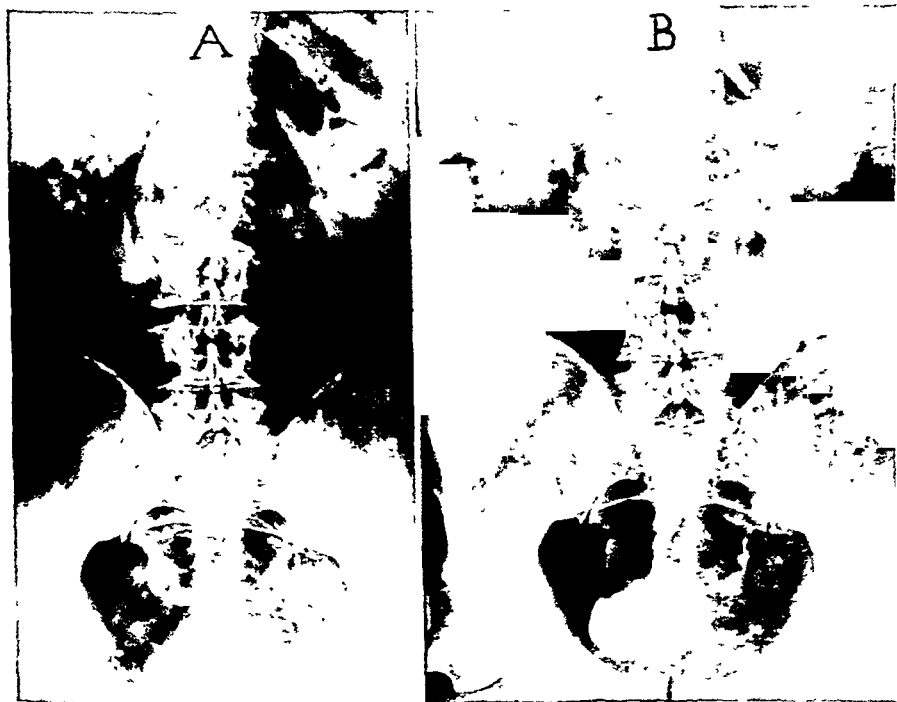


FIG. 2. Before and after segmental resection for papillary carcinoma of bladder. Hematuria 1 year. Tumor size: 3 by 3 by 1.5 cm. Grade 2, underlying bladder invaded depth 0.1 cm. Two recurrences on re-examination 3½ years later requiring total cystectomy. Death ½ years after initial surgery from acute pyelonephritis.

In 1 case a recurrence developed and when the patient was examined 3½ years after the initial surgery, he was found to have two large tumors of the bladder. He was treated by total cystectomy with implantation of the ureters into the sigmoid. While the initial result seemed to be satisfactory, fulminating bilateral pyelonephritis developed 3 months later and the patient died approximately ½ years after the initial surgery.

In summarizing the results in this group of tumors, three are alive and well without further treatment. 9, 11 and 11 years respectively. Two are without evidence of recurrence at this time following multiple fulgurations, 2 and 3 years respectively; and one patient is dead of acute pyelonephritis following cystectomy ½ years after initial surgery, a mortality rate of 16½ per cent.

The second group of 8 cases were large tumors and situated close to or in-

volved one of the ureters. The largest weighed 147 gm., and measured over 5 cm. in gross diameter. The smallest weighed 30 gm.

All of these patients had noticed hematuria varying from 3 weeks to 6 years' time, except one who had had no hematuria but had complained of left lumbar pain over a period of 3 months' time

Two of these individuals were treated by segmental resection of the bladder and nephrectomy. One is alive without further treatment 17 years following surgery, and the other was well and free of recurrence for 5 years. At that time he died of a cardiac infarct.



FIG. 3. Before segmental resection. Large papillary carcinoma of bladder. Later, right nephrectomy for multiple cortical abscesses. Hematuria 3 months. Tumor size .3 by 3 by 2 cm. Grade 2. No postoperative x-ray available. No recurrences. Death from cardiac infarct, 5 years later.

Six patients were treated by segmental resection of the bladder and re-implantation of the affected ureter into the base of the bladder, the ureter being splinted for from 5 to 7 days with a No. 6 ureteral catheter.

Of this group, one patient died on the fourth postoperative day of a massive pulmonary embolism. The remaining five are alive and well, 1, 2, 4, 6 and 11 years respectively.

In one of these patients a small recurrence developed on the trigone 5 years after surgery and was fulgurated elsewhere. The patient is reported to be free of any evidence of malignancy at the present time.

Of the entire group of 14 cases, nine have had no evidence of recurrences vary-

ing from 1 to 17 years; six, from 5 to 17 years. In three, recurrences that have developed have been treated by transurethral fulguration; and of the remaining two there was one hospital death, and one died following cystectomy, a mortality rate of 14 per cent and an incidence of recurrence of 22 per cent.

#### DISCUSSION AND CONCLUSION

Large papillary tumors of the bladder have been known to exist in the bladder for long periods of time, the longest in my own experience 6 years, and to have attained considerable size as is shown by one tumor in this group which measured 8 cm. in greatest diameter and another which weighed 147 gm.

The assumption that large tumors may be of a low degree of malignancy is suggested by a history which may date back several years, by the fact that such tumors have not metastasized in spite of their long presence in the bladder, also by their loose texture often evident on cystogram and cystoscopy, and by the presence of a relatively small pedicle.

As more knowledge of the behavior of bladder tumors is accumulated, it has become evident that the degree of anaplasia and the depth of invasion of the bladder wall determine curability to a greater degree and that the type of surgery to be employed should be adjusted to these factors.

Of the 9 tumors on which complete pathological data were available, three proved to be grade 1; three, grade 2; two, grade 3, and one, grade 4; and of this group, five showed superficial invasion of the underlying bladder wall. The one grade 4 tumor had penetrated deeply and into the lymphatic vessels.

The depth of invasion into the bladder wall may be the determining factor as to whether a cure will be obtained. Unfortunately this can be determined finally only by pathological examination of the specimen after the operation has been performed. Biopsy to determine the degree of anaplasia may imply such invasion if a grade 3 or grade 4 tumor is encountered and particularly if the tumor tends to be solid or to have a relatively wide base. In my opinion the importance of the biopsy is directly proportionate to the above factors and is relatively unreliable and impracticable in large papillary tumors of loose texture and with small pedicles.

In conclusion, this group of cases is presented in support of an opinion that any large single papillary tumor of the bladder wall with a long history verifying its presence there, or with other factors suggesting a low degree of malignancy, such as loose texture and relatively small pedicle should be treated by conservative surgery. Radical surgery need not be extended to this group.

*1117 Republic Bldg., Denver, Colo.*



## CARCINOMA OF THE BLADDER: A NEW SURGICAL APPROACH IN SELECTED CASES

THOMAS E. GIBSON

The following case report will serve as an illustrative example of the technical aspects of a surgical procedure which may occasionally be found useful in dealing with certain types of bladder tumors:

### CASE REPORT

A well developed, well nourished 55 year old man, a retired army major, presented himself with a history of intermittent gross hematuria of approximately 10 years' duration. The pertinent facts on examination were the finding of an enormous grade 2 papillary carcinoma occupying the base of his bladder at the site of the right ureteral orifice, practically filling the right half of the bladder. It was well localized, with a base approximately 3 by 4 cm. in dimensions and the surrounding bladder mucosa appeared normal. The Jewett procedure done under spinal anesthesia was negative as regards infiltration of the bladder wall. Excretory urography revealed a normal upper urinary tract (fig. 1, *A*). In personal experience, dilatation of a ureter caused by a bladder tumor is practically certain evidence that the tumor is not limited to the mucosa but has invaded the bladder wall. The absence of dilatation of the right ureter was therefore regarded as a favorable sign. Since the growth was too large for transurethral resection, at least in my hands, open operation was decided upon. Accordingly, on August 16, 1950, under pentothal curare anesthesia, a transvesical segmental resection of the bladder was performed. The steps of this procedure are shown in the accompanying illustrations (figs. 2, 3 and 4). It was impossible to locate the right ureteral orifice so it was disregarded during the subsequent procedure which consisted simply in widely encircling the growth with an incision involving the entire thickness of the bladder wall (fig. 2, *A*). Hemostasis was readily accomplished as the incision progressed. The resected block of tissue was then lifted into the bladder cavity with the ureter attached (fig. 2, *B*). The ureter was then sectioned at a convenient distance behind the bladder wall, and reimplanted at the upper end of the incision which was closed with interrupted sutures of chromic gut No. 1 (fig. 3, *E*). A ureteral splinting catheter was placed in the right ureter and brought through the urethra together with a Foley catheter (fig. 3, *F*). The two catheters were strapped together with adhesive external to the urethral meatus. The cystotomy incision was then closed about a de Pezzer catheter with interrupted chromic No. 1 sutures. The de Pezzer catheter was removed from the suprapubic incision the first postoperative day. The sutures in the suprapubic incision were removed on the eighth postoperative day. The urethral catheter and the ureteral splinting catheter were removed on the fourteenth postoperative day, after which the patient voided normally. Convalescence was remarkably smooth and uneventful.

Read at the annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 20, 1952.

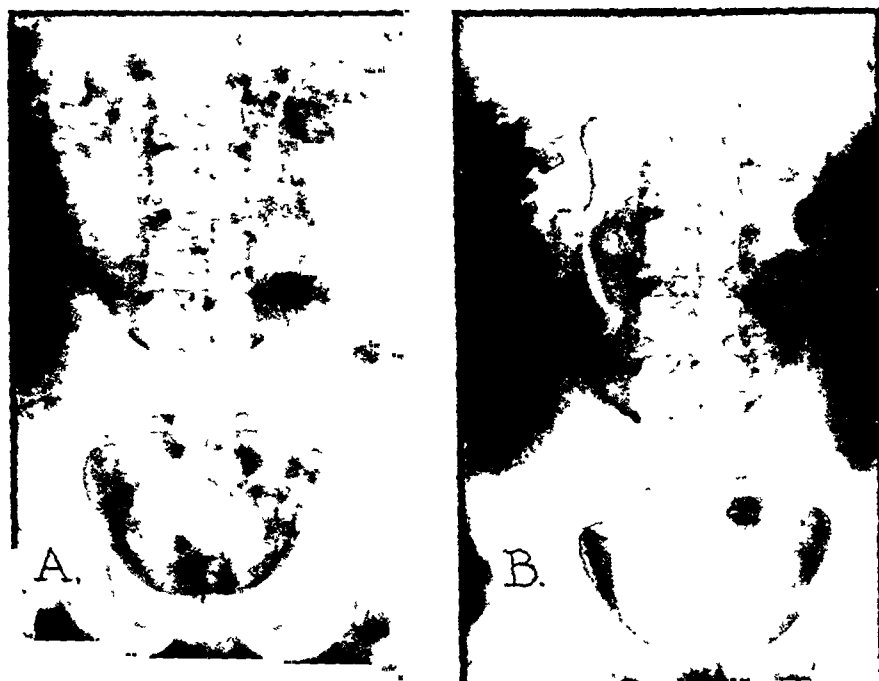


FIG. 1. *A*, preoperative excretory urogram showing normal upper urinary tract and large space filling defect on right side of bladder caused by intravesical papillary carcinoma, grade 2. *B*, retrograde pyelogram 6 weeks after intravesical segmental resection of bladder tumor and right ureterocystoneostomy showing normal right kidney and ureter

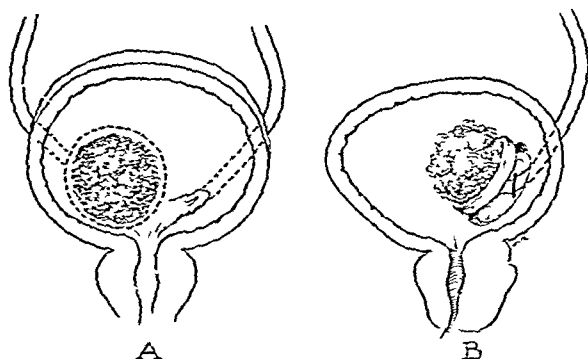


FIG. 2. *A*, schematic diagram of tumor covering site of right ureteral orifice as seen following suprapubic cystotomy. *B*, intravesical segmental resection of bladder wall circumscribing tumor with ureter still attached. Black line indicates point at which ureter was sectioned. Fatty retrovesical tissue is seen behind area of excision.

It occurred to me afterwards that it would have been safer to re-implant the ureter at a different site (fig. 4, *C*, *D*). However, cystoscopy with right retrograde pyelography was performed on September 27, 1950 (approximately 6 weeks postoperative) at which time the bladder appeared entirely normal, the re-implanted right ureteral orifice appeared patent and a catheter was passed to

the right renal pelvis without difficulty. A right retrograde pyelogram was performed, revealing normal appearing calyces, pelvis and ureter (fig. 1, B).

(This patient subsequently succumbed to a primary bronchogenic carcinoma which proved on exploratory thoracotomy to be inoperable. It was an independent growth unrelated to the bladder tumor.)

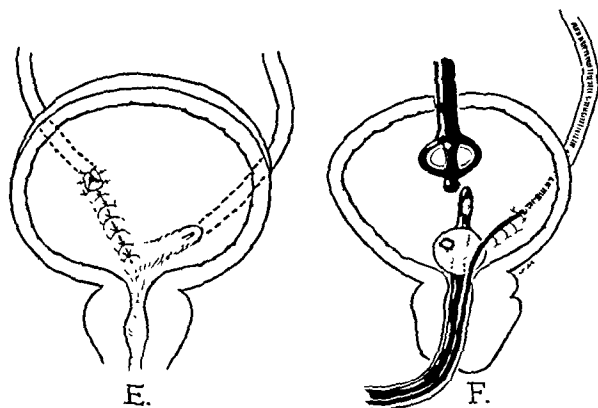


FIG. 3. *E*, defect in bladder closed with interrupted sutures of No. 1 chromic gut. Ureter re-implanted at upper end of incision. *F*, shows method of ureteral intubation and bladder drainage. Foley urethral catheter drains bladder and serves also to maintain ureteral intubation in proper position. Cystostomy wound is closed about a de Pezzer catheter.

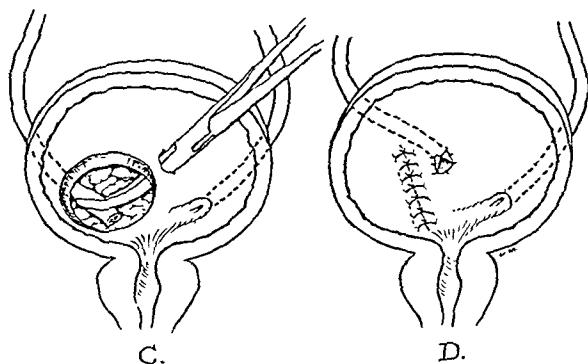


FIG. 4. *C* and *D*, schema illustrating alternate method of ureterocystostomy, probably preferable to re-implantation in area from which tumor has been excised.

Pathological report (microscopic): "The sections show a complex papillary structure which arises from the mucosa of the bladder. The fronds all have a fibrous core of varying diameter and are covered by heaped-up, transitional epithelium. The epithelium is rather well-formed, but the lesion penetrates the lamina propria of the mucosa to a slight extent. The mucosa in some areas is infiltrated by chronic inflammatory cells and rarely are there focal aggregates of these cells. The muscularis of the bladder is intact. Pathological diagnosis: Papillary carcinoma of the bladder, grade 2."

## COMMENT

For more extensive infiltrating growths involving larger areas of bladder wall the more radical standard technique of external mobilization and excision of the involved bladder wall must be utilized. This time honored procedure has in personal experience resulted in a sufficient number of long term cures to establish it on a firm foundation. The place of partial cystectomy in the treatment of bladder tumors has been well summarized in the textbook statement of Dodson:<sup>1</sup> "Resection of a segment of the bladder wall is applicable to all tumors so situated that the entire tumor can be removed with a margin of normal bladder wall and the wound so sutured that normal bladder function will be resumed. This method of treatment is not necessary in papillary tumors unless the bladder wall has been deeply infiltrated. Papillary tumors of grade 1 and 2 can be adequately treated by diathermy or the implantation of radium. Resection is best suited to tumors situated in the upper half of the bladder, but may be successfully executed in early infiltrating tumors in any part of the bladder. Involvement of the ureteral orifice complicates but does not necessarily preclude segmental resection. The ureter may be divided as it enters the bladder and reimplanted as near its normal location as possible when the bladder has been reconstructed."

The particular variant of segmental resection illustrated in this case report, which might properly be termed *intravesical segmental resection*, is applicable only in the occasional case, but is recommended because of its ease of performance and the smooth rapid convalescence of the patient.

Diathermy or transurethral resection of the tumor did not appear to be applicable in this case for several reasons, first of all, the bulk of the tumor mass, second, the involvement of the ureter which would have suffered injury by these procedures, and third, there was no way of telling definitely by any of the criteria at our command whether or not the bladder wall was invaded.

## CONCLUSIONS

Although the literature on bladder tumors shows a rather wide disparity of opinion as to the choice and efficacy of various methods of treatment, the operation of segmental resection or partial cystectomy is rooted on firm foundations.

A variant of this procedure termed *intravesical segmental resection* with uretercystneostomy is described as a method applicable to selected cases.

A bladder tumor involving a ureteral orifice with associated dilatation of the ureter is indicative of infiltration of the bladder wall. The absence of dilatation, while offering a more favorable prognosis, does not necessarily mean that the tumor has not infiltrated the bladder wall.

450 Sutter St., San Francisco Calif.

<sup>1</sup> Dodson, A. I.: Urological Surgery. St. Louis: C. V. Mosby Co., 1950, p. 533.

## THE SURGICAL TREATMENT OF TUMORS OF THE GENITO-URINARY ORGANS

ARCHIE L. DEAN

*From the Department of Urology, Memorial Hospital, New York, N. Y.*

A number of years ago, the writer presented a paper on "The Radiation Treatment of Tumors of the Genito-Urinary Organs." Here radiation played as important a role as possible in the treatment of each disease and every effort was made to relegate surgery to the status of an adjuvant or abandon it. Today, the young urologist finds such a viewpoint difficult to understand and in his pursuit of more extensive operations, neglects almost completely the limited but unique benefits of radiation. He may be assured, however, that the efforts to thoroughly explore and utilize the therapeutic possibilities of radium and the roentgen rays which, about 1920, began on a broad scale, were based on a determination to overcome failure of the surgery of that time to control genito-urinary tumors. After another 25 years passed with striking improvements in diagnostic urology, surgical technique, anesthesia, production and proved value of antibiotics and chemotherapy, and the use of unlimited transfusions, it was right that the urologist, so equipped, should re-attack the tumor problem to overcome the frustrations of radiation and radiation combined with conservative surgery.

The adoption of radical cancer operations by the urologist was justifiable because such treatment is suited to the natural history of these tumors and use of similar principles has produced the best results with neoplasms in other parts of the body. However, radical surgery for bladder tumors is far more complicated than radical operations on the breast or uterus which it attempts to imitate, because, in addition to extensive removal of tissue from a relatively inaccessible region, profound changes are made in the function of the kidneys and sometimes the bowel.

At present, the application of radical surgery to tumors of each of the genito-urinary organs is well established although, as yet, the operations are not standardized. Under the most favorable conditions, years must elapse before their true value will be known but their promise is apparent. At the Memorial Hospital, the writer continues to use all radiation methods of established value but radical surgery is employed at every appropriate opportunity. This presentation will be limited to present surgical practices. They may be short lived because they are subject to change as soon as other methods prove better. No end results, as yet, can be given but the goal is improved end results.

Radical operations for cancers of the genito-urinary organs should be designed to completely remove the primary tumor together with all adherent tissues, any possibly affected adjacent structures or organs, and at least the regional lymphatics. Operative manipulations should be performed as far as possible from the tumor. The growth should not be incised nor should its coats be weak-

Read at the annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 20 1952.

ened in any other way before its removal in toto. Operations such as these may be a great immediate tax on the patient; the function of essential organs other than that from which the tumor arose may be profoundly altered; even the way of life may be changed. It is essential, therefore, that the candidate for such surgery be strengthened by all effective physical measures. Psychic preparation also is important but usually no more is required than a reasonably optimistic description of life after any proposed changes in the disposition of the excretions. For these reasons, radical operations for tumors of the genito-urinary organs must be carefully planned well in advance.

The basis of good planning is accurate information of the nature and extent of the tumor and the general health of the patient. Although urological diagnosis is searching and is steadily improving, it seldom can provide complete information for ideal radical operations. However, if every diagnostic effort is always made, these deficiencies will diminish. Meanwhile, clinical judgment must substitute for each uncertainty.

Radical nephrectomy for a kidney tumor should consist of ligation of the kidney pedicle close to the great vessels before the growth is manipulated, removal of all perirenal fat with the tumor, and a clean dissection of the nodes and lymphatics about the great vessels as far cephalad as the diaphragm. Opening the vena cava to remove a tumor thrombus may also be necessary. These measures cannot be performed through the usual lumbar approach nor through a makeshift modification of it after an unsuspected neoplasm has been exposed. The procedure, therefore, must be planned in advance after making a clear-cut diagnosis.

Characteristic deformities of the pelvis and calyces due to pressure of an infiltrating and expanding intracapsular lesion usually suffice for the diagnosis of a kidney tumor. It is better to make the diagnosis certain because cysts often are radiographically indistinguishable from tumors, certain cysts do not require surgery, and the well conducted tumor operation not only makes no provision for diagnosing the primary growth at the operating table but avoids its neighborhood as far as possible.

Smith and his associates have shown the value and safety of aortography in differentiating kidney cysts and tumors. Recently, use of intravenous injections of larger quantities of more highly concentrated iodide solutions have provided nephrograms helpful in differential diagnosis but these pictures on the whole have not been as revealing as those following aortography. Microscopic examination of the urine from the affected kidney for desquamated cancer cells, when reported definitely positive by an experienced observer, may also call for the radical operation but unless these findings are unquestionable, the method may be misleading and time consuming. Removing tissue directly from the suspected tumor, in the writer's opinion, is the quickest, easiest, and surest way to prove its nature. Kidney aspirations with an 18 gauge needle have been uncomplicated in a personal experience of perhaps 300 operations during more than 15 years. Unfortunately, urologists cannot fully utilize this valuable test because pathologists have been slow to learn to diagnose smears.

After the diagnosis has been established, one should choose the operation best

suit to fulfill all of the necessary postulates. The surgical approach for kidney tumors has been actively discussed since Sweetser analysed the methods used previous to 1946, and proposed an improved incision which has since been associated with his name. The usual lumbar incision was carried to the anterior midline caudad to the umbilicus and thence cephalad to the sternum. Through the transverse limb of the incision the kidney could be explored and if a tumor was found the vertical limb could be added. I have used this approach with great satisfaction. To me, at first, it was astonishing to observe how the vertical limb of the incision removed support from the tumor causing it to fall anteriorly leaving the pedicle exposed for early ligation. In addition, through this approach, the removal of huge growths was comparatively simple. Unfortunately, this incision does not provide unobstructed access to the lymphatics about the great vessels in the region of the diaphragm and the initial exploration to verify the diagnosis should no longer be part of a cancer operation.

A great advance was made when Chute began to popularize the thoraco-abdominal approach to kidney tumors. Subsequent reports from many sources unanimously described its safety, the ease with which the renal pedicle is exposed for ligation before the tumor is handled, the free access to the great vessels for lymphatic dissection, and the suitability of the incision for removing tumors of the largest size. This incision has always proved satisfactory and its use has produced no complications.

During the past 2 years, for kidney surgery generally, I have used the Nagamatsu incision, and for large tumors have modified it slightly. With the patient in the usual lateral posture, the incision starts from the interspace between the ninth and tenth ribs just lateral to the border of the sacrospinalis muscle. It is carried caudad above the angles of the three lower ribs until over the twelfth rib its direction is changed so that it parallels the twelfth rib as far as the anterior midline. An inch is then resected subperiosteally from the tenth and eleventh ribs just mesial to their angles and the twelfth rib is removed. When dealing with large tumors, I have carried the incision to the anterior midline and thence cephalad to the sternum. In this approach, as with the Sweetser incision, the anterior limb removes support from the mass and unless it is completely adherent it falls anteriorly exposing the pedicle. When the Nagamatsu incision has been completed, moderate traction on the rib and muscle flap exposes the kidney in the lower part of the operative field and provides free access to the entire sub-diaphragmatic region. After ligation of the vessels of the pedicle close to the aorta and vena cava and removal of the tumor, the exposure facilitates a careful, lymphatic dissection as far as the diaphragm. In fact, the dissection has been carried in the retropleural mediastinum for perhaps 7 or 8 cm.

While I have found this a satisfactory approach to kidney tumors and recommend its use, I do not believe that it is better than the thoraco-abdominal approach except that it is definitely less time consuming. In my limited experience, I have not found any procedure possible through the thoraco-abdominal incision that could not be done easily through the modified Nagamatsu. While the thoraco-abdominal approach has clearly shown urologists that the additional

hazard of opening the chest is slight, it should be avoided if unnecessary, just as the peritoneal cavity is not entered unnecessarily during the usual kidney operation.

Radical nephrectomy should be performed for Wilms tumor, tumors of the renal parenchyma in adults, and epithelial tumors of the pelvis. Preoperative radiation is never used. Postoperative radiation is always given Wilms tumors whether or not disease can be found beyond the kidney. In tumors of adults during removal of the regional lymphatics, if metastases are found, it is helpful to fasten metal skin clips at the site so that postoperative radiation can be directed more accurately.

In the absence of demonstrable metastases at operation, postoperative radiation is not given until recurrences appear because these tumors, as the result of their nature and deep location, require large amounts of radiation to induce any regression. Such treatment should not be given unnecessarily. Furthermore, routine prophylactic postoperative radiation probably is not highly effective in preventing recurrences, and by producing radiation changes in the superficial tissues, it prevents the administration of full tumor doses later should recurrences appear.

Operations on the bladder should also be planned well in advance so that patients can be prepared for exhausting procedures which may also involve diversion of the urine and perhaps changes in the bowel. With information now available, there should be general unanimity regarding the proper choice of patients for local treatment which conserves the bladder and radical surgery which diverts the urine and removes the bladder and prostate together with any other pelvic organ which may impede a clean lymphatic dissection. Many pathological examinations of excised bladders and pelvic lymph nodes have shown that 40 per cent of the tumors which have infiltrated the bladder muscularis have metastasized. This corroborates Jewett's reports on the increasing futility of conservative treatments as tumors infiltrate deeper. There is also ample laboratory verification of the clinical observation that palpable induration of a tumor base is presumptive evidence that the tumor has penetrated the bladder wall and that palpable thickening along the route of the bladder vessels indicates lymphatic metastasis. Unfortunately, when tumors have reached a stage that such diagnostic findings are clear cut, few cures can be achieved by any degree of surgical radicalism. The conclusion, therefore, appears inescapable that to cure patients with bladder tumors, every individual with an infiltrating growth must be considered a candidate for radical surgery.

A serious handicap lies in urological diagnosis which, good as it is, as yet is too crude to accurately show the status of the patient who is near the borderline of curability. Probably after the most careful preoperative examination there is a factor of error as great as 20 per cent in estimating the amount of disease outside of the bladder as well as within it. This was clearly shown by the study of 100 consecutive bladders removed for tumors. At the pathological examination of the entire bladder, 50 tumors were found to have a higher grade of malignancy than that shown in the cystoscopic biopsy. There were 11 cancers first diagnosed



as papillomas, and there was microscopic infiltration of tumor cells outside the bladder in 11 patients in whom direct examination by the surgeon had shown no evidence of disease. In an appraisal, therefore, of bladder tumor patients before operation, one must recognize the importance of this large factor of possible diagnostic error because it affects a sizable proportion of patients who occupy an intermediate position between those who may be treated successfully by conservative measures and those whose only hope may lie in radical surgery or palliation.

The realization of a large factor of diagnostic error has variously affected urologists. A conservative group which maintains that nothing better has been established, continues to use a number of agents within the bladder. I believe this position not only is unjustified at present but it promises little therapeutic improvement in the future. Some younger urologists, with excellent surgical training, believe that mistakes due to uncertainties of diagnosis are best minimized by broadening the field of radical surgery. As a result, they divert the urine and remove the bladder which, in many cases, could be saved. Few of the advocates of radical surgery have had much practical experience with conservative therapy and, as a result, the possibility of bladder preservation, I believe, is too seldom thoroughly explored. There is ample evidence that smaller and superficially infiltrating tumors can be controlled by treatment which conserves the bladder, while in the presence of metastatic disease it has not been demonstrated, as yet, that the patient benefits significantly from radical surgery. For these individuals, surgical palliation appears to offer the greatest benefit until radical operations establish a cure rate sufficient to outweigh the disadvantages of pyelonephritis, electrolyte imbalance, frequent tumor recurrence and problems of rehabilitation.

Transurethral resection has adherents, some of whom have attempted to build a complete system for treating bladder tumors of all sizes and types with the resectoscope. Unfortunately, this is futile because the scope of the instrument is restricted, limiting the most skilled resectionists to no more than local treatments. Furthermore, the cutting current frequently distorts the appearance of biopsy specimens so that a benign growth may look malignant and malignant tumors may appear benign. When used in the bladder the instrument is dangerous and it is undependable for completely removing extensive or deeply infiltrating cancers in the bladder wall; it does not treat metastases and it can not relieve ureteral obstruction.

Small superficial tumors do not enter importantly into this discussion because they can be treated successfully by conservative local measures such as electrocoagulation, implantation of radon seeds, segmental resection, or these treatments in combination. Occasionally, ureteral re-implantation may be required. Therefore, with the exception of multiple papillomatosis, which is unique and for which there is no effective local treatment, it should be considered a major error to remove the bladder for superficial tumors. In conjunction with efforts to preserve the bladder, close observation after treatment is essential. Local recurrences or new tumors are likely to spring up but if discovered early and treated promptly

their control should not be difficult. If not discovered promptly and energetically treated, preferably with electrocoagulation and radon seeds through a cystoscope, the earlier efforts to avoid radical surgery probably will be wasted.

After disposing of the relatively simple tumors as conservatively as possible, a much more difficult problem must be solved in treating the large and important group of patients with infiltrating bladder cancers. The extent, location, and type of these tumors may vary considerably but they are all serious. Their gravity is due not so much to their propensity to weaken patients with dysuria, hemorrhage, and obstructive pyelonephritis, for usually these factors can be remedied, but because, in addition, at the time of their discovery they are so frequently attended by metastases. Probably all of these patients require surgical treatment.

As it is a major error to remove the bladder unnecessarily, it is equally wrong to perform inadequate operations. In the treatment of infiltrating bladder cancers, first in the category of ineffectiveness I place simple cystectomy. Requiring also diversion of the urine, this becomes an extensive operation which can only be successful when tumors are confined to the bladder and local growths are frequently amenable to more conservative measures. After studying many patients treated with diversion of the urine and simple cystectomy and noting the frequent and early appearance of tumors in pelvic lymph nodes, it seemed evident that this operation could only be applied successfully to those exceedingly rare individuals with infiltrating tumors which can not be removed by segmental resection and which have not metastasized.

While in common with a number of other urologists, I routinely combine dissection of accessible pelvic and iliac nodes with bladder removal, failures of such measures produced need for a considerably more radical operation which, with the bladder, would remove all pelvic and lumbar lymphatics and any organ which interfered with such a clean dissection as well as any pelvic organs or tissues secondarily involved. Such an operation was reported by my associates Marshall and Whitmore who generally recommend the procedure for the treatment of extensive bladder cancers. I believe the operation represents sound radical surgery.

"The abdomen is opened through a long paramedian incision or a liberal transverse incision at the level of the anterior superior iliac spines, transecting both rectus muscles. If exploration of the upper abdomen (with particular reference to the liver and para-aortic lymph nodes) shows no evidence of metastasis outside the pelvis, and if exploration of the pelvis reveals the tumor to be locally operable, the patient is placed in a moderate Trendelenburg position and the small bowel is packed out of the operative field.

"The peritoneum overlying the common and external iliac arteries is incised on either side of the bifurcation of the aorta to the terminations of the external iliac arteries. The ureters and peri-ureteral tissues are mobilized from the pelvic brim to within 2 or 3 cm. of the bladder, where they are transected. The rectosigmoid and its mesentery are divided as close to the base of the bladder as is feasible. The dissection of the iliac lymph nodes begins bilaterally just above

the aortic bifurcation and extends to the terminations of the external iliac arteries. The dissected tissues are pushed mesially and inferiorly in continuity with the pelvic viscera.

"The obturator fossa is cleaned of its fat and lymph nodes, but the obturator nerve is preserved. Bilateral ligation of the internal iliac arteries at their origins has been carried out without demonstrable ill effects. The vasa deferentia are divided near the internal inguinal ring but the spermatic vessels can usually be retracted laterally and preserved. The posterior parietal peritoneum with the subjacent retroperitoneal tissues distal to the aortic bifurcation is pushed downward and the retrorectal plane in the hollow of the sacrum is opened by blunt dissection to the tip of the coccyx.

"The incisions in the posterior parietal peritoneum are extended from the terminations of the external iliac arteries to meet at the bladder vault. The anterior and lateral surfaces of the bladder are freed leaving virtually all the perivesical fat on the bladder. The posterolateral attachments of the bladder and rectum are divided, dissecting the lymph nodes and perivascular tissue from the internal iliac vessels and ligating the visceral branches of these vessels. Packing is frequently necessary to control venous bleeding until the dissection has been carried far enough to permit visualization of bleeding points.

"Bilateral uretero-intestinal anastomosis is carried out by placing the ureters in the same or in separate troughs in the rectosigmoid, employing the Coffey 1 technique. An end colostomy is constructed either through a separate stab wound or through the original incision. The wound is then closed in layers with chromic catgut, employing through-and-through, heavy, silver wire stay sutures. Two or three Penrose drains are placed in the pelvis through the inferior angle of the wound.

"The patient is then placed in the lithotomy position. The anal orifice is closed with a purse string suture and an elliptical incision is made encompassing the anus and adjacent skin. The membranous urethra (or indeed the entire bulbous urethra and triangular ligament) is dissected free and the puboprostatic ligaments are transected. The terminal portion of the rectum with a portion of the levator muscles is mobilized and the specimen is extracted. Closure of the perineal defect is effected by approximation of the levator muscles when possible, by closure of the subcutaneous tissue and skin, by packing, or by a combination of these methods. Packing against a small rubber dam has seemed effective and generally applicable. The ends of the Penrose drains previously inserted into the pelvic wound may be brought out through the perineum to provide through-and-through drainage.

"If the perineal phase of the procedure is omitted, the specimen can be removed through the abdominal route by dividing the puboprostatic ligaments and transecting the membranous urethra and the rectum at the level of the levator muscles. The rectal stump is then closed with chromic catgut and perineal drainage established by means of a stab wound adjacent to the anus. The ureterocolostomy is constructed and the abdominal wound closed as described.

"The ureterocolostomy is drawn 2 to 4 centimeters beyond the skin surface

and maintained there by three or four Halsted clamps, grasping the full thickness of bowel wall at 12, 3, 6, and 9 o'clock, and securely taped to the skin; or fixation may be obtained by suturing the bowel wall to the anterior rectus sheath.

"The operative specimen includes the bladder; prostate; seminal vesicles; perivesical fat; obturator, internal iliac, external iliac, and common iliac lymph nodes; and a variable segment of rectum including that adjacent to the prostate and bladder base together with the intervening tissues. At the conclusion of the operative procedure, the only structures visible in the pelvis are the muscles and bones forming the pelvic floor and walls, the iliac vessels, and the obturator nerves. No effort is made to reperitonealize the pelvis."

Such an operation represents an extreme effort to cure patients with bladder tumors so extensive as to be otherwise uncontrollable. At present, it is good experimental surgery. Whether or not such radical operations are justifiable can only be shown by future comprehensive studies of their operative mortality, postoperative morbidity, cure rate, and the usefulness of individuals so treated to themselves and to society. So far, little success has followed operations upon tumors with fixed or numerous metastases even though they were limited to the pelvis.

The following procedure is recommended in an attempt to discover more accurately the extent of disease and thus give each patient appropriate treatment. In this way, the possible advantages of radical surgery may be obtained when necessary and the disadvantages are not inflicted without reason.

After making the usual examinations to show the nature and extent of the tumor in the bladder, the condition of the upper urinary tract, and the patient's general condition including a chest roentgenogram, he is prepared for radical surgery. The choice of operation is not made, however, until after the peritoneal cavity has been opened and its contents examined, the peritoneum over the ureters incised, and the pelvic lymphatics and perivesical regions carefully inspected and palpated. If no enlarged nodes can be found and there is no evidence of induration beyond the bladder, segmental resection may suffice, or radon seeds may be embedded. It may be necessary to re-implant a ureter in the bladder. Clean dissection of the principal groups of lymphatics should always be done but removing the rectum to ensure a clean dissection when no enlarged nodes can be found should not be necessary. At the same time, one must guard against lessening the patient's factor of safety by undue conservatism. While segmental resection often can remove a tumor confined to the bladder as completely as can cystectomy, there is always danger of tumors appearing in the preserved portion. Segmental resection seldom is successful when there is tumor infiltration of the trigone, and since about 65 per cent of bladder cancers touch the trigone, segmental resection or any other conservative method should not be attempted for infiltrating tumors of the bladder base. In such cases, cystectomy and node resection should provide a greater cure rate. Similar treatment appears most suitable for multiple papillary carcinomas with involvement of a considerable portion of the bladder wall or growths near the urethral orifice.

If the direct scrutiny shows extensive or fixed metastases or dense adherence

of the bladder, palliative surgery should be used. Diversion of the urine immediately stops frequency and dysuria and relieves kidney obstruction. It usually diminishes hematuria for a time and may be followed by much tumor regression. Proper transplantation of the ureters is essential and much experimental and clinical study has been given the technique of uretero-intestinal anastomosis. Success requires the transplanted ureter to have the largest possible blood supply, to follow a straight course into the bowel and to be free from traction and compression. Probably the most efficient anastomosis provides a tunnel beneath the serosa and part of the muscular layer of the bowel and fixes the two structures by interrupted sutures which pass through the mucosa of the bowel and the entire wall of the split end of the ureter. After studying the clinical course of patients with uretero-intestinal anastomosis, a high proportion of whom showed normal excretion urograms, and after noting the frequency of pyelonephritis and electrolyte imbalance which often causes death, there is reason to believe that until these complications can be avoided or promptly cured, uretero-intestinal anastomosis should be reserved for palliation while cutaneous ureterostomy should be employed when a cure is likely. As soon as skin anastomoses are firmly healed, collecting cups should replace catheters because kidney infection is unavoidable with foreign bodies such as catheters, but sterile urine has been obtained with cups.

Probably when a prostatic cancer can be recognized by rectal palpation the patient is incurable. On the other hand, since no one can do more than guess at the nature of small areas of induration, diagnosis based on rectal palpation alone is attended by an unavoidable factor of error of at least 10 per cent. The examination of frozen sections removed by incisional biopsies at the operating table with all in readiness for radical surgery violates ideal practice by incising the growth, and diagnostic errors as great as 15 per cent have been reported following microscopic examinations of frozen sections. The Memorial Hospital experience with thousands of aspiration biopsies has demonstrated their safety and accuracy but the test has not been adopted generally because pathologists have been slow to study the diagnosis of tissue smears. The writer, who will not treat a patient for prostatic cancer unless the clinical impression is corroborated by microscopic evidence, performs biopsies by aspiration with a plain 18 gauge needle in every case.

There is common agreement that radical prostatectomy of some type should be performed when the growth is confined to the gland. Probably this principle can be broadened somewhat to include with benefit patients whose tumors can not be removed completely, because it permanently relieves obstruction of the bladder outlet. On the other hand, performing radical prostatectomies on patients with metastases which have regressed under hormone therapy may promote comfort but it does not increase the cure rate because disappearance of metastases continues only as long as hormonal control.

As soon as the diagnosis of an operable prostatic cancer has been made, estrogens should be given. It is desirable to obtain hormone control of the growth because there may be great biological differences, as yet clinically indistinguish-

able, in prostate cancers and some, when incised, pursue a wild, uncontrollable growth. After about 4 weeks of estrogen treatment, guided by reduction of the serum acid phosphatase to normal, or the appearance of feminization, the operation can be performed. Here again, the greatest benefit can be expected only from the well-planned cancer operation. As to which radical operation to choose, perineal removal is as good as any. The radical retropubic operation as yet has not demonstrated specific advantages.

As soon as a tumor of the testis has been discovered, it should be removed for microscopic examination on which subsequent treatment is based. Orchiectomy is so harmless and specific information regarding the tumor is so essential that this operation is recommended even in the presence of metastases. The immediate neighborhood of the tumor is carefully avoided by an incision overlying the spermatic cord which is ligated and severed near the internal abdominal inguinal ring. There appear to be no advantages in ligating the spermatic cord more proximally. Experience has shown that when the tumor is first recognized such a large proportion of patients have demonstrable or occult metastases in the pelvic and abdominal lymphatics that there is general agreement that these regions always should be treated. There are differences of opinion, however, as to what this treatment should be. The writer suggests that if the tumor is a seminoma, radiation alone should be sufficient to give prophylactic or curative treatment to the routes of lymphatic drainage or to any other part of the body. When choriocarcinoma is found, there is little to be gained by any further procedures because the disease spreads through the blood stream and it is radio-resistant.

With embryonal carcinomas, teratocarcinomas, or adult teratomas, after giving a tumor dose of 3500 r. to the pelvic, abdominal and epigastric lymphatics, a clean dissection of these structures may be performed. This operation is suggested in the hope of extending curative therapy because these tumors produce early and relatively radioresistant metastases. Although past experience has shown no significant benefit from surgery, former surgeons lacked the advantages of the newer exposures without which, even now, there can be little hope of success. A thoraco-abdominal approach made by removing the ninth rib can be extended to the depths of the pelvis. This facilitates complete and meticulous dissections from the diaphragm to the pelvis. The Nagamatsu incision also has given complete access to these retroperitoneal structures and in the writer's hands requires less time.

Since cancers of the penis, like other epidermoid cancers, metastasize by embolism, amputation a centimeter or a centimeter and one-half proximal to any visible or palpable tumor should completely remove the primary growth. While conservatism has no place in the treatment of metastases, I believe radical surgery should not be performed until the need is proved. In a study of several hundred men with penile cancers, palpable inguinal adenopathy was present in 80 per cent of the men at the time of their first examination. Biopsies and observation for ten or more years showed that of these enlarged nodes only one-half were cancerous. Since cancers of the penis usually spread first to accessible

inguinal or subinguinal nodes and grow slowly and since radical groin dissections cause varying degrees of disability of the lower limbs and most of these men are laborers, unnecessary groin dissections should be avoided.

When the patient has been anesthetized for removal of the primary tumor, any suspiciously enlarged or hard nodes should be aspirated. Such nodes may also be excised, but with cancer present there is considerable danger of fungation following partial surgical removal. If metastasis is not found by aspiration, the patient should be closely observed as long as he lives. If the nodes are cancerous, following removal of the primary growth a radical inguinal dissection should be performed. Leaving only essential blood vessels and nerves, all fat, fascia and lymphatic tissue are removed from the proximal third of the femoral canal to the junction of the common iliac veins. To facilitate operating in the pelvis, following dissection of the femoral and inguinal regions, the inguinal ligament is incised above the femoral canal giving clear exposure of the lymphatics accompanying the iliac vessels. Because this operation is long and tedious, it is best performed on but one side at a time. However, due to the crossed lymphatics at the base of the penis, inguinal metastasis usually is bilateral. Thus, when lymphatic dissection has been performed on one side, there is usually need to apply it to the other as well. Here again, however, I have seen no harm to the patient from waiting until close observation, verified by biopsy, showed that the operation was necessary. The relatively large proportion of patients who require skin grafting after radical groin dissections can be reduced if the wounds are closed by sliding full thickness grafts.

#### SUMMARY

Radical operations for tumors of the genito-urinary organs constitute a comparatively new aspect of urological therapy. To be properly performed they must be carefully planned in advance. This requires diagnoses more searching in some respects than present procedures provide. If uncertainties remain after careful examination, one can only be guided by the natural history of the disease and the best interests of the patient. While final evaluation of radical surgery for tumors of the genito-urinary organs lies far in the future, its furtherance by those who perform it capably appears highly desirable because of all present forms of treatment it gives the greatest promise of increasing the cure rate in these diseases.

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## LEIOMYOSARCOMA OF THE URINARY BLADDER: REPORT OF A CASE

ARTHUR B. CECIL

The picture of tumors of the bladder of mesothelial origin, both benign and malignant, is becoming clarified by the contributions of more and more observers reporting single cases. It is true that an occasional urologist has seen more than one case, but it is also true that many large clinics have never observed a single case.

It is easy to see, from a study of the literature, that those who have encountered these tumors have recognized that they were in the presence of an unusual growth. I shall limit this paper to a discussion of one particular group of mesothelial malignant tumors of the bladder, namely leiomyosarcoma. In 1939, Kretschmer and Doerhing<sup>1</sup> reported a case of leiomyosarcoma of the bladder, and summarized 14 cases from the literature. In 1943, Crane and Tremblay<sup>2</sup> added 7 cases from the literature, but did not include the case reported by Shivers and Henderson.<sup>3</sup> Other cases reported are one by Lev and Bell,<sup>4</sup> one by Mackles et al.<sup>5</sup>, one by Jones and Ross<sup>6</sup>, and one by Katzen.<sup>7</sup> The case which I am presenting is the twenty-eighth one of leiomyosarcoma of the bladder to be reported.

Even from this limited clinical material, certain conclusions can be drawn: leiomyosarcoma occurs at any age; it occurs in childhood, but not more frequently than in later life; it is more common in males than in females; it extends both locally and by metastasis. The prognosis is bad. The first symptom is usually hematuria, but dysuria follows as the growth increases in size, or as the bladder becomes infected, and the growth may obstruct either the urethra, the ureter or both.

The tumor may spring from any part of the bladder wall. It is many times pedunculated and lobulated, or it may be of broad base. Its surface to begin with is smooth, and this is striking upon looking at the tumor cystoscopically. Later it may become ulcerated and encrusted with lime salts. Leiomyosarcoma may be associated with other changes in the same tumor: osteogenic and carcinomatous changes have been reported. On cut sections the tumor has a collagenous appearance.

Malignant leiomyomas have been classified into three groups, the malignancy increasing proportionately: 1) those closely resembling leiomyoma; 2) those having short spindle-shaped cells with oval nuclei; and 3) those having great variation in the morphologic character of the cells.

Read at the annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 18, 1952.

<sup>1</sup> Kretschmer, H. L. and Doerhing, P.: *Arch. Surg.*, **38**: 274, 1939.

<sup>2</sup> Crane, A. R. and Tremblay, R. G.: *Ann. Surg.*, **118**: 887, 1943.

<sup>3</sup> Shivers, C. H. de T. and Henderson, K. P.: *J. Urol.*, **42**: 761, 1939.

<sup>4</sup> Lev, M. and Bell, W. E.: *J. Urol.*, **57**: 251, 1947.

<sup>5</sup> Mackles, A., Immergut, S., Grayzel, D. M. and Cottler, Z. R.: *J. Urol.*, **59**: 1121, 1948.

<sup>6</sup> Jones, H., Morus, M. C. and Ross, C. F.: *Brit. J. Surg.*, **38**: 242, 1950.

<sup>7</sup> Katzen, P.: *J. Urol.*, **67**: 518, 1952.



Cohen<sup>8</sup> states that the cells of this tumor are shorter and rounder than those of a benign tumor. The nuclei are massive and hyperchromic. Giant cell forms may exist. The stroma is scanty, and the walls of the blood vessels are defective. The occurrence of many mitotic figures is considered a reliable sign of malignancy.

Treatments that have been recommended have been wide excision of the tumor with diathermy cooking of the base, total cystectomy, deep x-ray therapy. It will require many more careful studies to determine the relative value of these procedures.

#### CASE REPORT

A man 58 years old was admitted to the Hospital of the Good Samaritan, Los Angeles, on March 4, 1951. His complaint was hematuria. The family history was negative for malignancy. With the exception of an appendectomy, which

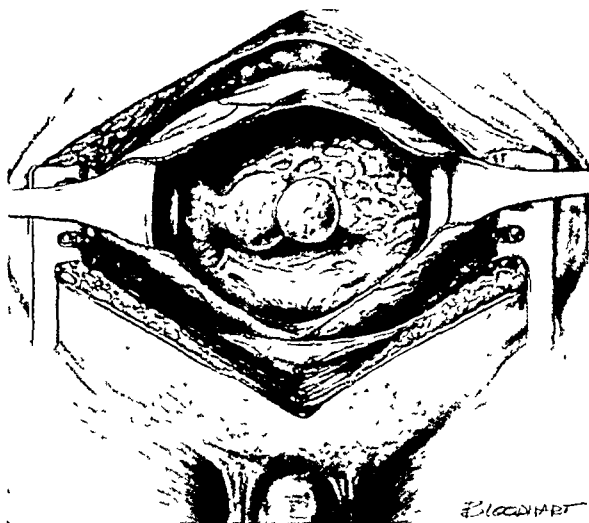


Fig. 1. Appearance of the tumor upon opening bladder. Note pedunculation and lobulation.

was done in 1939, he had been at work constantly for 32 years. Three years before admission he was taken with painless hematuria. He again had hematuria 1 month before admission, and 1 week before admission had hematuria which lasted 7 hours. The blood was the only symptom. The physical examination was negative. A flat film of the abdomen showed some calcified glands in the abdomen, and arthritic changes in the lumbar spine. The right inferior pubic ramus showed some expansion, and irregular coarsening of the trabeculation in the bone consistent with Paget's disease. An excretory urogram showed fair concentration of the dye in both kidneys, and the pattern of the upper urological tract was normal. The prostate was of normal size, somewhat firmer than normal, not malignant. The genitalia were negative. Blood count and blood smear were normal. Kolmer and Kline tests were negative.

Cystoscopy: "On the right side of the bladder wall, 4 cm. above the right ure-

<sup>8</sup> Cohen, J. S. - Arch. Path., 13: 857, 1932

teral orifice, is a rounded, smooth tumor mass which must be pedunculated, as it can be shifted around with the cystoscope. The mass seems to be about the size of an English walnut. When it is pushed aside the right ureteral orifice can be seen. The rest of the bladder wall appeared normal. A study of the prostatic border shows some intravesical enlargement of the prostate."

Operation (May 3, 1951): On the right side of the bladder wall was found a perfectly smooth tumor which was composed of two portions, one above another and each about the size of a five cent piece. This dumb bell like tumor had a pedicle of about 1 cm. breadth, and upon pulling up on the tumor a tent like portion of the bladder wall was raised up (fig. 1). The tumor was seized with a clamp to lift it up, but the clamp squashed right through it. The tumor was then wrapped with gauze and lifted up, and while tension was kept on it a diathermy cutting knife was used to widely excise the bladder wall around the base and deeply beneath it. After removal of the tumor the base was cooked with a dia-

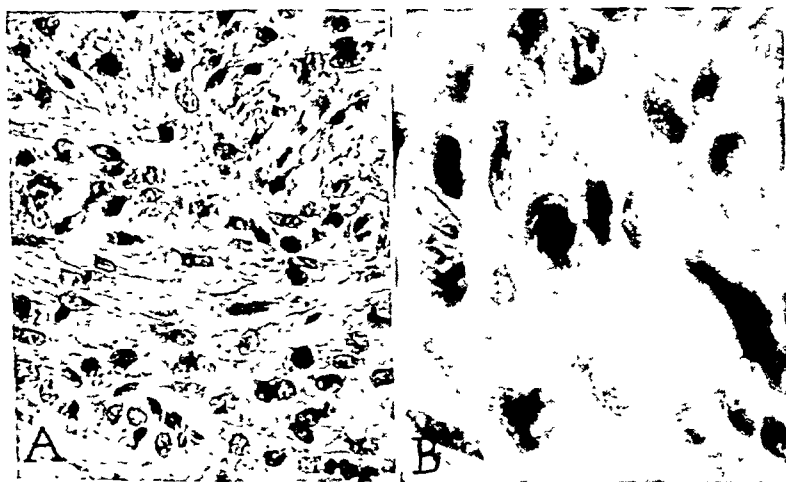


FIG. 2. A, leiomyosarcoma. B, leiomyosarcoma. Note spindle shape cells with variation in size and shape of nuclei, hyperchromatism and mitotic figures.

thermy current. Bleeding was astonishingly slight. A suprapubic drainage tube was put in and a Foley catheter through the urethra.

Surgical pathological report No. B2031-51 (Dr. L. J. Tragerman): "Specimen consists of resected portion of bladder wall, including a centrally placed mass. Total weight of the tissue is 16 gm. The periphery and base of the specimen are cauterized. The projecting mass is about 4 cm. in average diameter. Cut surface is fleshy, smooth, glistening, light tan with some yellow grey foci. Microscopic examination shows a spindle cell tumor with considerable variation in structure. This is produced by variation in degree of cellularity and by presence of many areas of degenerative changes. The tumor structure is best preserved in the area of increased cellularity. Here one sees the predominant cells to be spindle cells with oval to elongated fusiform nuclei. Cytoplasm is coarsely fibrillary and cell borders indistinct. The intracellular fibrils, often densest about the nuclei, give the blue staining reaction of myofibrils with the Mallory stain. In the most

cellular areas there is considerable variation in nuclear size and shape (fig. 2, *A*) and nuclei show both vacuolization and hyperchromatism. Mitotic figures are infrequent (fig. 2, *B*) and nucleoli mostly small. In the areas of less cellular to scanty growth there are marked degenerative and lesser inflammatory changes. These include zones of collagenous condensation and hyalinization of stroma, myxoid degeneration of stroma and focal, often perivascular, lymphoid infiltration. Blood vessels are prominent within the tumor, with frequently thickened walls. In some areas tumor growth blends with prominent muscle cells in small blood vessels."

"Sections at the periphery of the tumor show no capsular separation from bladder wall despite the gross polypoid growth. The pathological diagnosis: Leiomyosarcoma of low-grade malignancy."

Examination (June 4, 1952): Fifteen months following operation a careful examination showed no evidence of recurrence of the tumor in the bladder nor elsewhere in the body. The patient is in perfect health.

*1136 W. Sixth St., Los Angeles 17, Calif.*

## PRIAPISM DUE TO UNUSUAL METASTASIS FROM BLADDER CARCINOMA: CASE REPORT

L. N. BERARD AND JOHN E. BYRNE

*From the Department of Urology, St. Louis University School of Medicine, St. Louis, Mo.*

Scattered reports of priapism due to neoplastic infiltration of the penis have appeared in the British and American literature.<sup>1,2,3,4,5</sup> Hinman<sup>6</sup> in a review of 170 cases of priapism reported in 1914 found 2 cases to be due to primary neoplastic infiltration; metastatic infiltration failed to account for the condition in any of the cases in his series. Ikeda, Foley and Rosenow<sup>7</sup> reviewed the literature in 1943 on the subject of malignant priapism. They found 8 cases of priapism due to malignant involvement of the penis by a primary neoplasm; to this number, the authors added a case of their own. In the group of cases in which the priapism was due to secondary or metastatic tumor in the penis, they found a total of fifteen cases. The primary tumor in these cases was found to be: prostate, 5 cases; bladder, 4 cases; testicle, 2 cases; rectum, 2 cases; kidney, 1 case; and liver, 1 case.

In one of the previously mentioned cases, Kessel<sup>5</sup> reports a case of bladder carcinoma metastasizing to the corpora cavernosa. In this case, the initial involvement occurred in the distal segment of the penis. Following the development of a single metastatic nodule in the region of the glans penis, the entire penile shaft was soon involved in rapidly spreading tumor tissue.

The spread of bladder carcinoma to the penis is unusual. It seldom involves the prostate, the seminal vesicles or the urethra by direct extension.<sup>8</sup> It was originally felt that carcinoma of the bladder tends to remain localized. As early as 1881 Albarran<sup>9</sup> demonstrated lymph node metastasis from carcinoma of the bladder. Colston and Leadbetter<sup>10</sup> found distant metastasis in 61 per cent of their cases. Spooner<sup>11</sup> found metastasis to the retroperitoneal lymph nodes, liver, lungs, and bone in 29 per cent of 167 cases of bladder carcinoma that were said to have died from other causes than the malignancy. Baker<sup>12</sup> mentions 4 cases in which

<sup>1</sup> Peacock, A. H. Malignant priapism due to secondary carcinoma of the corpora cavernosa. *J Urol*, 49: 732-747, 1943

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<sup>4</sup> Peters, C. N. and Huntress, R. L. Priapism and chordee due to metastatic carcinoma of the penis, with prostate being the primary source. *J Urol*, 49: 810, 1938

<sup>5</sup> Kessel, J. S. Interesting case due to multiple carcinomatous nodules in the corpora cavernosa. *J Urol*, 32: 213-216, 1934

<sup>6</sup> Hinman, F. Priapism. *Ann Surg*, 60: 698, 1914

<sup>7</sup> Ikeda, K., Foley, F. E. B. and Rosenow, J. Malignant priapism secondary to carcinoma of the urethra. *J Urol*, 49: 732-747, 1943

<sup>8</sup> Ackerman, V. L. and del Regata, J. A. Cancer. Diagnosis, Treatment and Prognosis. St. Louis C. V. Mosby, 1947

<sup>9</sup> Albarran, J. Les Tumeurs de la Vessie. Paris. G. Steinheil, 1891.

<sup>10</sup> Colston, J. A. C. and Leadbetter, W. F. Infiltrating carcinoma of the bladder. *J. Urol*, 36: 669-683, 1936

<sup>11</sup> Spooner, A. D. Metastasis in epithelioma of the urinary bladder. *Tr. A. Genito-urin. Surg.*, 27: 81-89, 1936

<sup>12</sup> Baker, W. J. Discussion of paper by Dean, A. L. and Ash, J. E. *J. Urol*, 63: 618-624, 1950.

bladder carcinoma developed penile metastasis following surgical treatment of the bladder tumor. All 4 cases had a different type of malignancy, and in all 4 cases the patients received some form of treatment to their obstructed bladder outlet, prior to, simultaneously, or shortly following surgical treatment of the bladder tumor. He points out the possibility of rapid penile metastasis following the invasion of recently operated prostatic tissue.

#### CASE REPORT

A 68 year old white executive was first admitted to the urological service by one of us (L. N. B.) on August 15, 1949. His initial complaint was that of frequency of urination and nocturia of 8 years' duration. The patient was known to have had a residual urine in excess of 6 ounces for the past 4 years, but on many occasions he had denied permission for surgery. In the 3 months prior to hospitalization his frequency had increased to hourly voiding, and he was getting up 5 to 6 times during the night. Except for the foregoing, his genito-urinary history was negative. He had always been in good health, and there was no familial history of cancer.

Physical examination disclosed a rather emotional, elderly white man who did not appear to be ill. The positive clinical findings revealed blood pressure 180/100 without signs of cardiomegaly or congestive heart failure. Examination of the abdomen was negative. Rectal examination disclosed grade 2 hypertrophy of the prostate without evidence of fixation or malignancy. The genitalia were negative, the penis was uncircumcised, and both testicles were in the scrotum free of enlargement or tenderness. The urethra was unobstructed to the passage of a 20F soft rubber catheter; 4 ounces of grossly clear residual urine. The initial urinary cultures were sterile. All of the laboratory examinations including the nonprotein nitrogen and the acid and alkaline phosphatase determinations were within normal limits. Cystoscopic examination on August 22, 1949 revealed median bar type of prostatic obstruction, and an irregular, granular area of necrotic tissue on the bladder wall just below the right ureteral orifice. Our initial impression was that of carcinoma of the bladder, type undetermined, and median bar prostatic obstruction. On August 26, 1949, a transurethral resection of the prostatic bar, and a biopsy of the suspicious bladder mucosa was performed. Bimanual rectal examination under anesthesia at this time failed to demonstrate a palpable lesion of the bladder. The pathological report on the resected tissue was that of benign prostatic hyperplasia and epidermoid carcinoma of the bladder, grade 1. The patient was markedly relieved of his symptoms following surgery, and although informed of the malignancy he refused further surgery at this time. The patient was discharged from the hospital 10 days following operation.

The patient was not seen again until November 1949, when he again returned complaining of increasing frequency and severe dysuria of three weeks' duration. He stated that he had noticed "tissue shreds" in his urine in the past 8 days. He gave no history of hematuria following the previous postoperative period. The patient was again hospitalized; his physical examination and laboratory determinations were unchanged from the first admission. He had 1 ounce of rather dirty

residual urine. Culture revealed an *E. coli* infection. Excretory urograms revealed good function and apparently normal renal outline. Cystoscopic examination revealed the area of resected prostate to be well healed with an adequate bladder outlet. The previously noted tumor mass had changed little since the previous observation. It was a single broad base tumor, approximately 0.5 cm. in its greatest diameter, and surrounded by a low ridge of necrotic tissue.

The patient was advised of the need for radical surgery, but again refused. On November 30, 1949 the tumor was resected transurethrally, and the base of the tumor fulgurated. At the time of surgery, bimanual rectal examination failed to reveal evidence of extension of the tumor through the wall of the bladder. The pathological report on the resected tissue was epidermoid carcinoma of the blad-

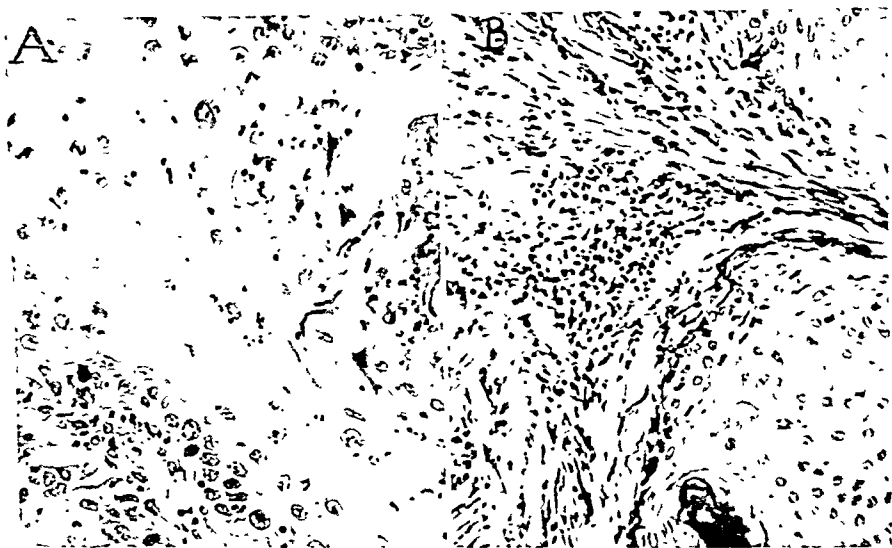


FIG. 1. A, section of bladder tumor removed transurethrally 3 months following initial biopsy. Again showing an epidermoid carcinoma, grade 1. B, section taken from indurated area in shaft of penis. Note extensive invasion of squamous tumor cells in architecture of penis. Further sections from this area showed involvement of corpora spongiosum as well as the cavernous bodies.

der (fig. 1, A). The postoperative period was uncomplicated, and the patient was discharged from the hospital on December 3, 1949. He was not seen again until April 1950, when he came to us complaining of severe dysuria, frequency, and periodic hematuria of 10 days' duration. He stated that for 3 days prior to consultation he had been experiencing persistent and painful erections. The patient was again hospitalized. Physical examination disclosed that he had failed miserably since the previous examination. He had lost 20 pounds in weight, was pale, and markedly dehydrated. Examination of the heart and lungs was not remarkable. The abdomen was soft, and no mass could be palpated. Examination of the genitalia revealed the penis to be semi-erect, and generally firm and tender (fig. 2). The penis was firm from a point just behind the corona, to the level of the suspensory ligament. In the midpoint of the shaft of the penis, there was noted

an area of greater density than the remainder of the organ. This area was approximately 2 cm. in length, and extended through the entire cross-section diameter of the penis. Rectal examination disclosed that the prostate had changed little in size or position, although at this time it was quite tender to palpation. Tender areas of induration were present over each seminal vesicle.

Laboratory examination revealed anemia ( $2\frac{1}{2}$  million red blood cells with 7 grams of hemoglobin). The nonprotein nitrogen was 60 mg. per cent. Urinary culture revealed a moderate growth of *E. coli*.

Excretory urograms revealed mild right hydronephrosis with delayed emptying of the dye on the right; the left side appeared normal. X-ray examination of the chest failed to reveal evidence of metastatic lesion.

Supportive therapy was begun upon admission to the hospital. He was given three transfusions of 500 cc each of whole blood with the correction of the anemia over a period of 5 days. Parenteral fluids were given with correction of the initial dehydration. Dihydrostreptomycin 0.5 gm. 4 times daily for 5 days produced sterile urinary cultures on the fifth day.

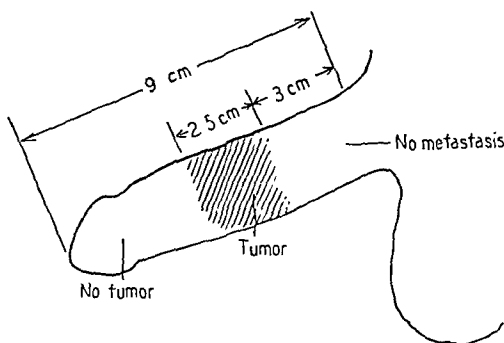


FIG. 2. Diagrammatic representation of localization of metastatic tumor in shaft of penis.

Cystoscopy under anesthesia 7 days after admission revealed an extensive tumor involving the entire base of the bladder, and obstructing the right ureteral orifice. Rectal examination disclosed invasion of the prostate and seminal vesicles.

The patient was requiring large doses of opiates for the relief of pain; in the face of the extensive local extension of the tumor we believed that we had little to offer him other than a palliative cystectomy and diversion of the urinary stream to the colon. The patient was prepared with oral urinary and gastro-intestinal antiseptics for 7 days. His appetite was good, he was no longer anemic, and his hydration was excellent. On May 8, 1950, under cyclopropane anesthesia, a total cystectomy with removal of the prostate, seminal vesicles, and the regional lymph nodes was carried out. The tumor had extended into virtually all of the pelvic structures, and the dissection was tedious and time-consuming. The ureters were anastomosed to the lower sigmoid in a mucosa to mucosa fashion, without splinting catheters. Both ureters appeared normal at the time of surgery. In the face of our preoperative impression of metastatic neoplasm in the penis, the organ was removed at its base.

The patient tolerated surgery poorly and showed signs of shock during the late stages of the operation, and in the immediate postoperative period.

Blood pressure stabilized following the administration of multiple whole blood transfusions and plasma. He was given both penicillin and streptomycin in therapeutic dosage and parenteral fluids were administered for the first 3 postoperative days. Urinary output through a de Pezzer catheter inserted in the rectum was 500 cc in the first 12 hours postoperatively. Urinary output subsequently increased to an average 1500 cc daily and maintained itself at approximately that level for the next 4 days. On the fourth postoperative day the patient had chills, fever, and appeared septic. He responded to the antibiotics on the seventh day and was temperature free. Little or no change occurred in the urinary output during the period of sepsis. After this period, the urinary output was increased to 2500 cc daily, the patient was ambulatory and tolerating food and fluids well. He was evacuating the bowel of urine every 2 to 3 hours during the day and 3 to 4 times during the night. Pathological report on the surgical specimen revealed a grade 4 epidermoid carcinoma of the bladder, with extension to the prostate and the seminal vesicles. Fifteen of twenty lymph nodes examined were involved by the tumor. Serial sections through the penis revealed the interesting feature of this case.

Sections taken from the base of the penis showed normal penile architecture without evidence of tumor. Sections taken from the previously described area 3 cm. from the base of the penis revealed dense tumor infiltration of the corpora cavernosa and the corpus spongiosum. The area of infiltration extended towards the distal end of the penis for a distance of 2.5 cm. (fig. 1, B). Serial sections taken from the shaft of the penis distal to the above segment, and from the glans penis failed to reveal further evidence of tumor. The patient had been doing well except for periodic bouts of low-grade temperature elevation, when on his twenty-fifth postoperative day he complained of sudden sharp pain in his chest, he expired within 30 minutes of the onset of pain. An autopsy was performed, and evidence of a recent anterior myocardial infarction was found. Scattered areas of metastatic epidermoid carcinoma were present in the lung fields, but no other evidence of tumor extension could be demonstrated. The ureterosigmoidostomy was intact, and the kidneys showed only moderate hydronephrosis. There was evidence of chronic pyelonephritis bilaterally.

#### DISCUSSION

A case of priapism due to metastasis of a bladder carcinoma to the penis is reported. This case is unusual not only in the pathological process, but even more so in consideration of the mechanism of the metastasis. In analyzing the case carefully, all of the known routes of metastatic spread were considered. The chance of direct implantation of this tumor by urethral instrumentation is, in our minds, more than a theoretical consideration.

In view of the pulmonary metastasis found at autopsy, the blood borne route of tumor spread would seem quite logically responsible for the penile lesion. This is not justified on two counts. First, there was no previous vascular thrombosis



or obstruction which could conceivably localize tumor emboli in a single segment of the penile shaft. Secondly, had the tumor been blood borne it would seem more likely for the involvement to have occurred in the terminal portion of the organ. The tumor emboli localized in the end vessels as was shown in other reported cases.<sup>5</sup>

The fact that the base of the penis was free of tumor would rule out the possibility of the bladder tumor extending into the resected prostate, and thence into the penis. Retrograde lymphatic extension although certainly a possibility does not seem likely in the absence of gross edema or microscopic evidence of lymphatic distention.

To further the argument of direct implantation of the tumor is the fact that this patient had been instrumented many times with large caliber instruments (24-28F) since the demonstration of the original lesion. The likelihood of such instrumentation denuding the urethra and lacerating the mucosa is obvious. The lacerated urethral mucosa offers an excellent medium upon which the displaced squamous tumor cells could lodge and proliferate. The involvement of the corpus spongiosum as well as the corpora cavernosa lends more weight to the theory of direct implantation of the tumor.

This pathological entity, although certainly a rarity, is of serious implications. Instrumentation of the urethra in any form is to be kept at a minimum in the face of a bladder neoplasm.

Our thanks are expressed to Dr. Walter Rice of the Department of Pathology of the St. Louis University School of Medicine for his aid in the interpretation of the pathological sections. Our thanks also to Mr. Phillip Conrath of the Department of Medical Illustration of the St. Louis University School of Medicine for his aid in the preparation of the illustrations.

## THREE UNUSUAL CASES OF PROSTATIC MALIGNANCY: ADENOCARCINOMA WITH MUCUS CELLS; MALIGNANT LYMPHOMA; LEIOMYOSARCOMA

GEORGE GILBERT SMITH

*Case 1. Mucus-cell adenocarcinoma of the prostate.* C. D. C., aged 34, married, advertising solicitor, was admitted January 20, 1949.

This young man was referred to me by Dr. R. D. Howell of Indianapolis with the following history:

The patient had been married 7 months previously. He had been in good health until the summer of 1948, when he noted generalized malaise, easy fatigability, anorexia with nausea and loss of weight. He noticed afternoon flushing of his face and an elevated temperature. During this period of time, he also had vague backaches, and other pains throughout the muscular system. No symptoms referable to the genito-urinary system were noted except occasional periods of frequency with some burning on urination but with no hematuria or pyuria. In the fall of 1948 the patient passed some tissue in his urine. In November 1948, he was admitted to the hospital where a tumor of the prostatic urethra was found. Dr. Howell resected the tumor at the bladder neck, and when the pathologist reported this to be carcinoma, he referred the patient to me for a possible total prostatectomy.

The past medical history and family history were unimportant.

Cystoscopy at the New England Deaconess Hospital on January 4, 1949 showed a normal bladder. In the prostatic urethra, which in general appeared smooth and lined with normal mucosa, there was a small, feathery, papillary tumor rising from the floor of the urethra about half way between the bladder neck and the external sphincter. Proximal to this was a necrotic elevated body which looked like a tumor that had been destroyed. The prostate by rectum did not feel remarkable.

The microscopic slides made from tissue resected by Dr. Howell in December 1948, were submitted to Dr. Benjamin Castleman, then assistant chief pathologist of the Massachusetts General Hospital. He said he did not consider the tumor very malignant. It was a tumor which formed glands and among the cells there were many goblet cells which strongly resembled those found in the intestinal mucosa. He thought that these tumors were probably rests from the intestinal mucosa which had, in the process of development, been included in the prostatic urethra.

My advice to Dr. Howell was that the visible tumors should be thoroughly electrocoagulated and the patient should undergo cystoscopy every 2 months. Dr. Howell carried out these suggestions, but about two months later dysuria developed, accompanied by a feeling of pressure in the perineum, slight terminal hematuria, and the passage of tissue in the urine. On April 13, 1949, the patient returned to Boston for further treatment.

Read at the annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 18, 1952.

Excretory pyelograms, a barium enema, and sigmoidoscopy showed no abnormalities. Further resection of the prostatic urethra was done April 16, 1949, the urethrorectal septum being cut down to a thickness of 0.5 cm. A papillary tumor removed from beneath the overhanging bladder neck proved to be a low-grade carcinoma with a high degree of differentiation (fig. 1). The prostate felt small and soft.

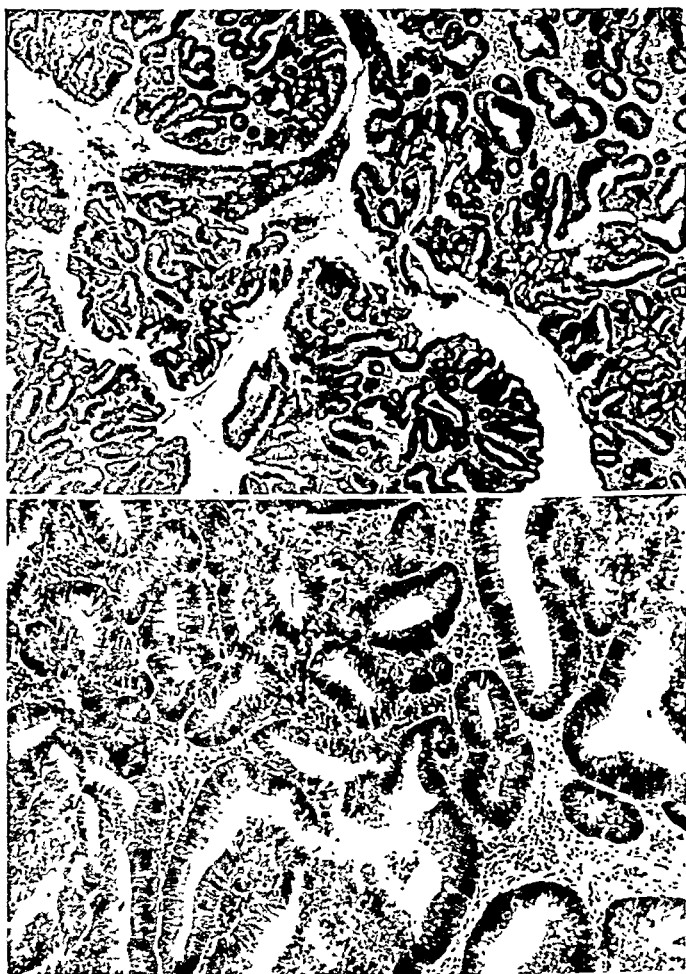


FIG. 1. Case 1. (Upper), mucinous adenocarcinoma of prostate, low power. (Lower), mucinous adenocarcinoma of prostate, high power.

The entire removal of the prostate in this young man, married for only a few months, was something that was to be avoided if possible. There seemed a fairly good chance that all the tumor had been removed by transurethral resection, but after consultation with Dr. Marks, radiologist at the New England Deaconess Hospital, it was decided to subject the prostatic urethra to radiation.

On April 22, 1949, a steel needle with a wall 0.3 mm. thick, containing 108

mg. of radon, was placed in a brass capsule with a wall 0.5 mm. thick. The capsule was placed in a Foley catheter just proximal to the balloon. The catheter was placed in the urethra, the balloon distended and the catheter drawn down as far as the balloon would permit. The catheter was left in place for 10 hours, thus giving a dosage of 1080 mg. hours. The patient was discharged 2 days later, having shown very little reaction to the radiation.

A note from Dr. Howell dated May 17, 1949 stated that the patient had had considerable urethral and rectal irritability.

The patient was cystoscoped by me four times, at intervals of a few months, the last time being 1 year after the radium treatment. At this cystoscopy there was no evidence of recurrence of the carcinoma. The mucosa of the prostatic urethra was still slightly eroded and covered with a thin layer of fibrin.

A letter received from Dr. Howell on June 18, 1952, stated that the patient had had occasional attacks of frequency and pyuria, improved by sulfonamides. He was last cystoscoped in February 1952, at which time there was no evidence of recurrence of his tumor. His prostate felt normal. He has stress incontinence. His sex life is very satisfactory.

True mucinous carcinoma of the prostate is very rare. No mention of this type of cancer was found in Ewing's *Neoplastic Diseases* (1940) or in Willis's *Pathology of Tumours* (1948). In the discussion of an article on adenocarcinoma of the bladder by Mostofi, Thomson and Dean in the *American Journal of Pathology*, Saphir asked if there are carcinomas of the prostate which are mucinous in type. Mostofi said, "We have seen a rare carcinoma of the prostate which is mucus-producing."

The treatment of this case may be open to question. The alternative to radium treatment would have been a radical prostatectomy. Against this was the probability that the tumor had invaded the bladder neck; with the ureteral orifices located on the lower edge of the trigone, removal of this area could not have been carried out adequately without transplantation of the ureters. Furthermore, the extent to which the cancer involved the membranous urethra was uncertain. The effects of radiation extended as far as the external sphincter.

Even if radical prostatectomy had removed all of the cancer, the patient would have been rendered impotent, a deplorable condition for a married man in his middle thirties.

The dosage of the radium application seems to have been as great as was consistent with safety to the rectoprostatic septum. Tissue destruction was not excessive, yet the effects of radiation were evident in the rectal mucosa.

*Case 2. Malignant lymphoma of the prostate.* F. S. aged 57, married, a school teacher, was referred to me by Dr. Joseph H. Lipton of Lynn to whom I am indebted for the following notes: "The patient consulted me on February 10, 1948, with a history of frequency, dysuria, and nocturia of two weeks' duration, culminating in marked urgency and hesitancy. Examination at this time revealed the prostate to be loaded with pus and there was a residual of six ounces.

"The patient was admitted to the Lynn Hospital, where on March 3, 1948, a transurethral resection was performed. The diagnosis was 'extremely ana-

plastic carcinoma of the prostate.' Laboratory work was as follows: nonprotein nitrogen 29, phenolsulfonphthalein, 65 per cent in 1 hour, acid phosphatase 0, and alkaline 3.0 King-Armstrong units. X-ray of the spine and pelvis showed no evidence of metastases.

"The patient was placed on stilbestrol therapy following the discovery of the carcinoma. He has not done well postoperatively, continuing to have marked frequency, urgency, and nocturia. On my examination on April 15, the gland, which had previously appeared very innocent to the palpating finger, had begun to take on a very firm feel to the palpating finger.

"I hope that total extirpation of the malignancy may be effected."

The patient had never been sick before his present illness.

April 23, 1948, the patient entered the Baker Memorial Unit of the Massachusetts General Hospital. Chest films showed no evidence of metastatic disease. Cystoscopy showed nothing remarkable aside from the results of the transurethral resection.

On April 26 a radical perineal prostatectomy was done. The vesicles were surrounded by firm tissue which did not resemble malignant growth; only the lower halves were removed. The membranous urethra appeared thicker than usual and there was a rim of thickened tissue extending about the bladder neck. This was removed as was a piece of the membranous urethra. Both showed only chronic inflammation. The prostate weighed 31 gm. Sections of the gland showed the cut surface to be firm, white, and nodular.

The microscopic examination as recently reviewed by Dr. Benjamin Castleman is as follows: "Microscopic examination shows extensive infiltration of the prostate with small ovoid to round cells with very little cytoplasm. The cells resemble lymphocytes, but are a trifle larger and have round to ovoid nuclei. Scattered mitoses are present. A striking feature of the distribution of the cells is their presence around the glands without destroying their lining cells. This is in sharp contrast to carcinoma which under similar circumstances would almost certainly destroy the glandular structures." The diagnosis was malignant lymphoma, lymphocytic type (fig. 2).

The patient's convalescence was uneventful except for thrombophlebitis in one leg for which he had bilateral vein ligation.

Beginning June 8, 1948, a course of deep x-ray therapy was given with the 200 KV machine. 8600 r. were given through five fields. In March 1949, rectal examination showed a definitely hard area on the left; on the right, a sheet of induration extended down to the perineum. He was given a second series of x-ray treatments, the million volt machine being used. An estimated tumor dose of 2000 r. was given through opposing anterior and posterior pelvic ports.

I saw him last on May 23, 1952. A stricture had developed in the region of the external sphincter and required monthly dilatation. Cystoscopy showed no evidence of recurrence of the tumor. He felt well, voided easily, and had only half an ounce of residuum. He continued to have poor control but only in the late afternoon. His weight was normal. No enlarged nodes were detected in his neck,

abdomen, or groins. On rectal examination there was soft induration in the prostatic area; this induration did not involve the perineum and the upper border was within easy reach. It is 3 years since his last x-ray treatment and over 4 years since his prostatectomy; he feels well and continues to follow his profession.

*Case 3. Leiomyosarcoma of the prostate.* L. D. T., aged 45, married, a printer, had had several children's diseases, but no other illnesses. For the past 3 years he had felt tired and had noticed excessive thirst, polyuria, and pruritus. He was found to have diabetes which was considered by the Joslin Clinic to be mild. He had had slight loss of weight.

He was referred by the Joslin Clinic to Dr. Theodore Pratt because of hemorrhoids. Dr. Pratt found his prostate to be enlarged and hard, and referred him to me.

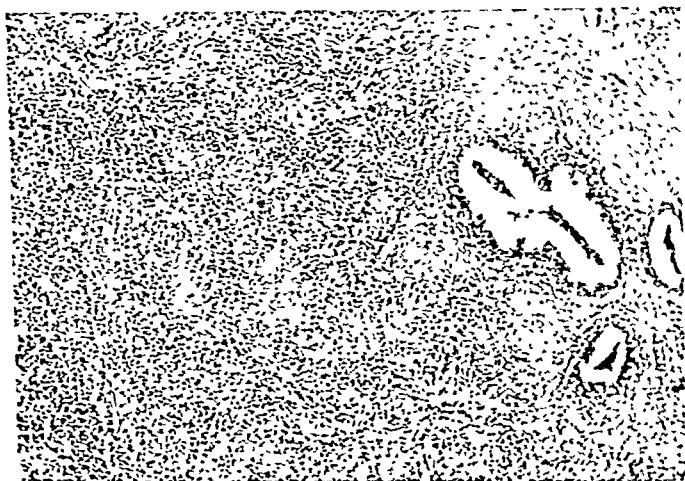


FIG. 2. Case 2. Lymphosarcoma, lymphocytic type, of prostate.

December 30, 1949, rectal examination showed that the prostate was firm, especially in the upper half. The left vesicle was very hard, cylindrical in shape, and about 0.5 cm. in diameter. I thought that, in spite of the patient's age (45), his prostate was malignant. The Cell Laboratory found tumor cells in the urine.

Cystoscopy (January 1, 1950) showed the bladder to be normal in appearance except for a smooth elevation of the left half of the trigone. The mucosa over the prominence appeared normal: the left ureteral orifice was seen at the upper border of the elevation and functioned normally. A metastatic series and intravenous pyelograms taken January 3, 1950, showed nothing abnormal.

On January 5, 1950, total perineal prostatectomy and vesiculectomy were done. When the trigone was exposed, the elevated area seen at cystoscopy was again identified. The edge of the trigone was cut across and the trigone easily freed from the underlying tissue. The left vesicle was removed with the prostate, the right vesicle separately. So far as could be ascertained, all malignant tissue was removed.

Pathological report: "The prostate gland weighs 62 gm, with one attached seminal vesicle. The gland measures 6 by 4 by 3 cm, is ovoid, with exteriorly adherent fibromuscular tags. Cut surface shows the posterior lobe to be replaced by hard, white, homogeneous tissue with yellow areas which extended into the attached seminal vesicle and the other lobes with poorly defined boundaries



FIG 3 (Upper), leiomyosarcoma of prostate, low power (Lower), leiomyosarcoma of prostate, high power

Microscopic diagnosis. Undifferentiated malignant tumor extending into seminal vesicle. Some foci suggestive of sarcoma" (fig 3)

Because of the nature of the growth, it seemed advisable to give the patient a course of x-ray treatment. This was supervised by Dr. Joseph H. Marks. With the 200 KV machine, 2100 r were delivered to each of four pelvic parts with the

beam directed towards the prostatic area. This series of treatments was completed on March 1, 1950.

Rectal examination on February 7, 1950, showed a rather firm, smooth sheet of tissue extending from the perineum upwards for about 2 cm.

The patient was last examined on June 5, 1952, two and one-half years after operation. He looked and felt well and was symptom-free. No masses were palpable in the pelvis or abdomen; his chest film on June 7, 1952, was normal. By rectum a hammock-like induration, smooth and fibrotic in character, could be felt extending across the rectum 2 cm. above the perineum.

#### DISCUSSION

There are a number of excellent articles on sarcoma of the prostate. From those of W. Kaufmann and A. W. Wright (1941), Melicow, Pelton and Fish (1949) and King and Cox (1951) the writer has culled the following statements and opinions.

The first case reported, a lymphosarcoma, was that of Coupland in 1877. Up to 1943 about 200 cases of sarcoma of various types were reported. Melicow et al. state that the incidence of sarcoma is approximately 1 in 1000 prostates removed for benign hypertrophy or carcinoma. All the articles on this condition emphasize the fact that sarcoma of the prostate is essentially a disease of youth, although it has been reported in a man 88 years of age. Culver's series showed a range of from 8 months to 77 years; 25 per cent occurred after the fiftieth year.

The possibility that sarcomas may originate in the prostate has been questioned, but N. Fukase, in a study of 222 prostates, found that small, primitive, or rudimentary lymph nodes occur normally throughout the gland. Kaufmann and Wright state that they have often seen lymphoid tissue in prostate glands.

The growth tends to extend into the periprostatic tissue and to metastasize to distant lymph nodes. The course as a rule is rapidly fatal.

Acceptable cases of leiomyosarcoma and of lymphosarcoma are not numerous. Prince and Vest have found 15 cases of leiomyosarcoma, including their own, which they accepted as originating in the prostate. King and Cox list 17 cases of lymphosarcoma verified by autopsy and seven, probably genuine, in which the diagnosis was based upon a biopsy.

Opinions differ as to the relative value of surgery and radiation. Bumpus, Culver, Sargent, Young, Randall, Ferguson, and Hess agree that surgery hastens the end. Many of the cases reported were subjected to transurethral resection and some to suprapubic enucleation. Vest, in 1940, removed by radical perineal prostatectomy a leiomyosarcomatous prostate; 1 year later the patient was in excellent condition.

In reviewing the results of the treatment of prostatic sarcomas by x-ray, one is not impressed. As a rule the improvement is only temporary. I am quite convinced, however, that the x-ray treatment to which cases 2 and 3 were subjected was of material help in controlling the disease. I doubt if radiation therapy alone would have given so satisfactory a result, but I feel quite certain that as an adjunct to surgical removal of the major part of the growth, it has considerable value.



## SUMMARY

Three cases of unusual types of prostatic malignancy are reported. A mucous-cell adenocarcinoma of the prostate in a man of 34 appears to have been controlled for at least 3 years by the application of 1080 mg. hours from radon applied intra-urethrally.

A lymphosarcoma, lymphocytic type, in a 57 year old man has been controlled for 4 years by total prostatectomy followed by deep x-ray therapy.

A leiomyosarcoma in a 45 year old man has been controlled for 2 years by total prostatectomy plus x-ray therapy.

In my opinion, neither operation nor radiation therapy alone would have been so effective as the combination of these methods of treatment.

I am grateful to Dr. Benjamin Castleman, pathologist at the Massachusetts General Hospital, for the microphotographs of case 2 and for his description of the cellular pathology. My thanks are due also to Dr. William A. Meissner, pathologist at the New England Deaconess Hospital, for the microphotographs of cases 1 and 3.

*1101 Beacon St., Brookline 46, Mass.*

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## BILATERAL ADRENALECTOMY FOR CARCINOMA OF THE PROSTATE GLAND: PRELIMINARY REPORT

WILLIAM J. BAKER

*From the Urological Services of Cook County and St. Luke's Hospitals, Chicago, Ill.*

Bilateral adrenalectomy has been used by us in patients whose carcinoma of the prostate gland and symptoms have not been controlled by open prostatic surgery or revision of the obstructive vesical neck, estrogens, bilateral orchiectomy, with and without deep roentgen therapy. The indications have been limited to the patient who has so much metastatic pain that regular doses of analgesics and sedatives have been required. These patients are miserable physical specimens. It was reasoned that any relief or well being which could be obtained from bilateral adrenalectomy without too much mortality or morbidity would justify the production of Addison's disease.

The problem of expense to the patient must be considered. The many laboratory studies before, during and after the procedure are very expensive. The cost of replacement therapy is between 60 cents and a dollar a day. The span of life after the procedure will probably vary a great deal. Therefore, the total cost of replacement therapy will vary likewise.

The next problem is related to the pre- and postoperative care of these patients. It must be admitted that our lack of mortality, complications and low morbidity is due to the skillful management of these patients by a very cooperative and faithful internist. The management of patients with Addison's disease is a real chore and must be considered seriously. The outline of our management is similar to that of Huggins and Bergenstal and is as follows:

- 1) Check date of surgery with urological service.
- 2) The day before surgery:
  - a) Cortisone acetate, intramuscular, 50 mg. at 6 a. m., 12 noon, 6 p. m., and 12 midnight.
  - b) Desoxycortisone, intramuscular, 5 mg. at 6 a. m.
  - c) Enteric coated sodium chloride tablets, oral, a total of 5 gm., as follows: gm. i at 5 p. m., 6 p. m., 7 p. m., 8 p. m. and 9 p. m.
- 3) The day of surgery:
  - a) Cortisone acetate, intramuscular, 150 mg. at 7 a. m.
  - b) Desoxycorticosterone, intramuscular, 5 mg. at 7 a. m.
  - c) During surgery, intravenous, 500 cc 0.9 per cent saline, 500 cc plasma.
  - d) After surgery:  
Cortisone acetate, intramuscular, 50 mg. q. 4 hours.
- 4) First day after surgery:
  - a) Cortisone acetate, intramuscular, 50 mg. q. 6 hours.
  - b) Desoxycorticosterone, intramuscular, 5 mg. at 8 a. m.
  - c) Enteric coated sodium chloride tablets, oral, gm. i, t. i. d.
- 5) Urological service will take note of the following when the postoperative orders are written:

Read at the annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 19, 1952.

- a) It would seem desirable not to give patient morphine or other opiates before surgery.
- b) The patient should not receive morphine or other opiates after surgery.
- c) If sedatives are needed, 50 mg. doses of demerol are preferred.
- d) Blood pressure readings will be recorded every 2 hours for 2 days after surgery.
- e) Daily determination of blood sugar, and serum sodium and potassium will be made for 1 week after surgery and twice a week thereafter.

The further management of these patients, if there are no other complicating endocrine disturbances, can be outlined as follows:

#### BASIC REQUIREMENTS

##### 1) Diet:

Moderately high carbohydrate, high protein and low fat.

Prolonged fasting is not well tolerated.

A gain in weight is usually not desirable unless there has been considerable weight loss.

Extra sodium chloride in the diet. Liberal use of salt at the table or salt tablets.

Adequate fluid intake.

##### 2) Cortisone:

Daily requirements about 25 mg. daily, orally, morning and evening. Additional 12.5 mg. or 25 mg. for periods of stress.

Some patients need only 12.5 mg. daily and others 37.5 mg. twice daily. The total dosage must be individualized.

Desoxycortisone acetate is usually not necessary.

#### INSTRUCTIONS TO THE PATIENT

The management of a patient with surgically induced adrenal insufficiency presents problems which are analogous to the management of a diabetic. The patient should be educated in the same way so that he may maintain proper daily control and meet any emergency which might arise.

The patient should be provided with an identification card which states his condition and the amount of cortisone which he is receiving. The name of his physician and hospital should be stated with instructions to take the patient to the hospital in the event of any crisis or sickness. The patient is told that if he experiences a sudden weakness or collapse, nausea or vomiting, to swallow one cortisone tablet and then telephone his doctor.

It has been found advantageous for the patient to keep a notebook of his daily progress in which he notes how he feels each day, any unusual pain or discomfort, weight, amount of cortisone, salt tablets and estrogen used, and the result of his urine test for sugar. When the patient is seen for a follow-up visit, his physician can record the weight and blood pressure in the patient's notebook. If this notebook remains with the patient, it affords the patient a certain protection if he is seen during a crisis by another physician.

## TECHNIQUE

The surgical removal of an adrenal is not difficult under the following conditions. Considerable time is allowed the anesthetist to give intratracheal anesthesia. This permits easy repair of the pleura without drainage, if a surgical rent of that structure is made. It was decided to remove one adrenal at a time to permit adjustment of these poor risks to the procedure and disturbed physiology. The second adrenal is removed about 2 weeks later. It has been argued that to remove one adrenal at a time makes the physiological studies more difficult. We have not found this so. It does eliminate a 24 to 72 hour bedside vigil by the internist. In three instances, the patients felt so well after the removal of one adrenal, that they did not want the second one removed. The remaining adrenal gland, when it was removed, was larger than the other adrenal gland. The patient is placed in the kidney position. An incision is made along the twelfth rib and this structure is removed. The upper pole of the kidney is mobilized enough to bring the renal pedicle into view. This incision permits a full view of the adrenal gland and easy management of all blood vessels to the region. The arterial blood supply of the adrenal varies a great deal but the arteries are usually small and produce no troublesome bleeding. The adrenal vein is usually large and must be ligated carefully. The anesthetist is ready to give intravenous adrenalin if the systolic blood pressure falls below 100. This has never happened. In two instances, the pleura was opened at its external lower angle but was easily repaired and no complications followed. The right adrenal gland is usually higher and more difficult to remove. The wounds are closed with drainage. There has been good healing in all instances. One wound abscessed after the patient had gone home. This wound has continued to drain for 9 weeks. It now appears that this wound will heal completely.

It was reasoned that oral estrogens should be continued because there are 1.7 to 8 mg. per diem of urinary 17-ketosteroids present after the testes and adrenals have been removed. It is reported that oral cortisone breaks down to leave a variable small amount of measurable urinary 17-ketosteroids. It is believed that the continuous administration of estrogens has prevented refractory patients after bilateral adrenalectomy. Five milligrams of oral stilbestrol 4 times a day have been used.

Ten patients have had bilateral adrenalectomy without operative mortality. Nine of these patients are living at this date. There was a positive tissue diagnosis of carcinoma of the prostate gland in all patients. Each patient had rather widespread metastatic bone lesions. Two patients had multiple lung metastases at the time of bilateral adrenalectomy. The preoperative serum alkaline phosphatase values were greatly increased in all patients. The preoperative serum acid phosphatase value was increased in one of these patients only. The postoperative serum alkaline phosphatase values varied from 3.6 to 36.1 Bodansky units. The postoperative serum acid phosphatase values were unchanged. The preoperative urinary 17 ketosteroids per diem varied from 0.7 to 12.5. The postoperative urinary 17-ketosteroids per diem varied from 0.7 to 8.3. Both adrenal

| RACE                                 | AGE | RELIEF OF PAIN AFTER FIRST ADRENALECTOMY             | RELIEF OF PAIN AFTER BILATERAL ADRENALECTOMY  | NARCOTICS REQUIRED               | SURVIVAL TIME                  | RESULT                                                                                                                                             |
|--------------------------------------|-----|------------------------------------------------------|-----------------------------------------------|----------------------------------|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| T. P. Negro.<br>St. Luke's Hospital  | 48  | Pain disappeared for 10 days.                        | 6 months<br>Occasional twinges and stiffness. | None                             | 6 months                       | Good. Has intermittent twinges from his multiple metastases. General condition is very good. Active and ambulatory.                                |
| I. S. White. Cook County Hospital    | 59  | Pain lessened.                                       | 22 days                                       | After 28 days.<br>Demerol B.I.D. | 5 months                       | Poor. Has multiple bone metastases, especially in cervical vertebrae. Becomes depressed when taking too much cortisone. Not active and is failing. |
| C. G. Negro. Cook County Hospital    | 61  | Complete cessation of pain.                          | 4½ months                                     | None                             | 4½ months                      | Excellent. Euphoric. Feels fine and has no complaints. Active and ambulatory.                                                                      |
| B. T. W. Negro. Cook County Hospital | 47  | Complete cessation of pain.                          | 27 days                                       | Demerol Q.I.D.                   | 3½ months.<br>Died May 7, 1952 | Poor. Metastatic lesions developed in every tissue and organ.                                                                                      |
| J. M. Negro. Cook County Hospital    | 57  | Complete cessation of pain.                          | 43 days                                       | None. Nembutal for sleep.        | 3½ months                      | Good. Requires sleeping tablets. Is home, active and ambulatory.                                                                                   |
| A. N. White. St. Luke's Hospital     | 65  | Pain greatly lessened.                               | Minimal discomfort.                           | After 60 days.<br>Demerol B.I.D. | 1 month                        | Good. Before adrenalectomy was bedfast with much morphine and 1 quart of Scotch daily. Now leads an active social life on cortisone and demerol.   |
| S. G. White. St. Luke's Hospital     | 76  | Complete cessation of pain.                          | 3 months                                      | None                             | 3 months                       | Excellent. Takes care of an invalid wife and runs a campaign to nominate Taft.                                                                     |
| E. N. White. Cook County Hospital    | 60  | Original pain disappeared. Right sciatica developed. | Right sciatica persists.                      | None. Uses salicylates.          | 2 months                       | Fair. Right sciatica bothersome. Active and ambulatory. In better condition than he was before adrenalectomy.                                      |

|                                     |    |                                |         |      |         |                                                                                                      |
|-------------------------------------|----|--------------------------------|---------|------|---------|------------------------------------------------------------------------------------------------------|
| C. B. White, St.<br>Luke's Hospital | 62 | Complete cessation<br>of pain. | 6 weeks | None | 6 weeks | Good. Patient has multiple<br>metastases and appears pal-<br>lorous and wasting. Not<br>very active. |
| J. Z. White, St.<br>Luke's Hospital | 51 | Complete cessation<br>of pain. | 3 weeks | None | 3 weeks | Excellent. Active and ambula-<br>tory. Well nourished. No<br>complaints.                             |

glands of two patients contained metastatic carcinoma. All other adrenal glands were normal in their histology. Orchiectomy by us means a removal of the testis and spermatic cord. In one spermatic cord, a complete adrenal gland was found. So, this patient had three adrenal glands removed. His preoperative urinary 17-ketosteroids per diem were 12.5. The operation has caused no oliguria. One patient, during early postoperative days, urinated 5 pounds of urine in one night. The screening test with ACTH was performed on each patient 2 weeks after bilateral adrenalectomy and was negative in each instance. The uric acid-creatinine ratio was not determined.

One preoperative reaction to cortisone has been noted. The patient had had his right adrenal gland removed. Two weeks later, at 6 a. m., he was given 150 mg. cortisone intramuscularly preparatory to the removal of his left adrenal gland at 8 a. m. Ten minutes after he had received the cortisone, he became very disturbed and tried to jump out a fourth-floor window. The patient in the next bed, who had had a bilateral adrenalectomy, made a flying tackle and saved a life. Two days later, the same dose of cortisone did not disturb the patient.

The following observations are of interest. Bilateral adrenalectomy has not caused any metastatic lesions to disappear. A few of the metastatic lesions appear more sclerotic or eburnated. New metastatic lesions continue to develop. It is noteworthy that new metastatic bone lesions have a tendency to produce stiffness and numbness instead of pain.

Two patients of low intelligence stopped taking estrogens and had a return of severe metastatic pain. As soon as estrogens were resumed, they were quite comfortable. Estrogens, previous to bilateral adrenalectomy, had not controlled metastatic pain.

No marked blood pressure changes or adrenal crises have been noted in these patients. One fellow, who is quite socially active, feels better on  $2\frac{1}{2}$  mg. desoxycortisone acetate a day, along with his daily dose of 25 mg. cortisone acetate. Otherwise desoxycortisone acetate has not been necessary.

In general, all of these patients are euphoric. One patient becomes depressed when he is receiving too much cortisone. No personality changes have been noted.

In case 6 a megacolon developed; the patient has formed stools 18 inches long and as big around as the forearm.

Three patients have developed occasional generalized edema. The internist has supervised their salt intake carefully. The edema will disappear when one dose of mercurhydriin is used. No notable deleterious effects have followed use of this mercurial diuretic. The edema will reappear in one to three weeks in these patients.

One patient has died. B. T. W., a Negro, 47 years of age, the youngest individual of our series, was the first to die. He lived  $3\frac{1}{2}$  months after the bilateral adrenalectomy. Autopsy revealed generalized metastases. No tissue or organ was without a metastatic lesion. He was free of pain for 27 days after adrenalectomy. He then required analgesics. Deep x-ray therapy seemed to control his pain. Less amounts of narcotics were required after the x-ray therapy. He wished to go home April 20, 1952. However, he was showing moderate generalized edema

which was controlled for about a week at a time with one injection of mercurhydrin. He complained of stomach cramps April 29, 1952 and was sweating profusely. Salt and potassium citrate were stopped for 48 hours. The cortisone was increased to  $12\frac{1}{2}$  mg. every 6 hours. The stomach cramps and sweating stopped. His appetite began to dwindle. Leg paralysis developed May 8, 1952. A spinal puncture gave no positive information except a positive Pandy test for albumin. Acute urinary retention developed and a marked adynamic ileus with very loose stools. He became stuporous on May 13, 1952 and all supportive treatment was not helpful. His blood pressure became 78 systolic and 40 diastolic and could not be raised. He was pronounced dead on May 17, 1952. The paralysis was explained at autopsy when a metastatic lesion was found in the spinal cord at the level of the fifth lumbar vertebra. Bilateral adrenalectomy afforded a 27 day period of freedom from the metastatic pain. The metastases continued to form and were extremely general. It is believed that the choice of this patient for bilateral adrenalectomy was poor because metastases were too general before the procedure.

The results of our work and the condition of the patients at the present time are shown in table 1. We are impressed with the comfortable states of the majority of these patients. The patients who now require small amounts of analgesics are leading a more comfortable existence than they did before bilateral adrenalectomy. One patient, whose pain returned, was given a short course of deep x-ray therapy over the painful region with good effect. It is emphasized again that this study has been done over too short a time to draw conclusions about longevity and the final course of the entity. A future report will be made on this work.

Appreciation and credit are given Drs. Edwin C. Graf, Daniel H. Callahan, Jr., Carl Hedblom, David Pressman, Carlin Chenoweth, Duane Greenfield and John Vandenberg, all of whom have been associated with me, in this study.

*7 W. Madison St., Chicago 2, Ill.*



## TESTICULAR NEOPLASMS: AN ANALYSIS OF 113 CASES

D. A. CULP

*From the Department of Urology, State University of Iowa, University Hospitals,  
Iowa City, Iowa*

The following is an analysis of a series of 113 consecutive cases of tumor of the testis seen at the University of Iowa Hospitals in the period from 1930 to 1950, inclusive. During this same period 179,899 males were admitted to all services of the hospital, and 23,870 to the urological service. Therefore, this disease accounted for 0.063 per cent of all male admissions and 0.47 per cent of the urological admissions during this same period. Rolnick found these neoplasms comprised only 0.5 per cent of all malignant tumors, while Hinman reported that 1 out of 1600 male admissions had a testicular tumor. This compares very closely with our figure of 1 out of 1592. Thus, it is evident that testicular neoplasms comprise a very small percentage of the patients seen in the average civilian hospital.

The age incidence is illustrated in figure 1.

The etiology of testicular neoplasms remains unknown. Nevertheless, the role of trauma and cryptorchidism as possible predisposing factors has been greatly emphasized. There was a history of trauma prior to the onset of a mass in 28 of the 113 patients, or 24.7 per cent. Some of these had recurrent injuries, but the vast majority had one traumatic incident followed in one to three months by the removal of a malignant mass from the scrotum. It is our opinion that the trauma in these cases did not play an important role in the development of the neoplasm, but probably did attract the patient's attention to the presence of the tumor.

In order to determine more accurately whether the incidence of neoplasm is higher in the undescended or in the descended testes, the percentage of neoplasms that were seen and the percentage of undescended testes that harbored neoplasms were determined. In the 20 years this study covered, 505 cases of cryptorchidism were reported. Four of these, or 0.79 per cent, exhibited malignant changes. During the same period there were 179,899 male admissions to the hospital. From this number 109 cases of testicular tumor were collected. This was 0.0605 per cent. Therefore, in this group, malignant changes occurred thirteen times more frequently in the undescended testis than in the normally located one.

Patients with testicular tumors presented themselves to us in one of two ways. The first group comprised the majority, 82.3 per cent, and came complaining of a painless swelling of the testis. The second group had symptoms referable to the metastases from the primary lesion (table 1). The incidence and location of the metastases in this group of 113 patients at the time they were first seen are illustrated in table 2. Of the 113 patients studied, 81, or 71.6 per cent already had metastases at the time of the first examination. The sites most commonly encountered were retroperitoneal, 73 cases (figs. 2, 3, 4); lungs, 40 cases (fig. 5); cervical lymph nodes, 12 cases, fig. 6; mediastinal lymph nodes, 6 cases (fig. 6); and bones, 13 cases (figs. 7, 8, 9).

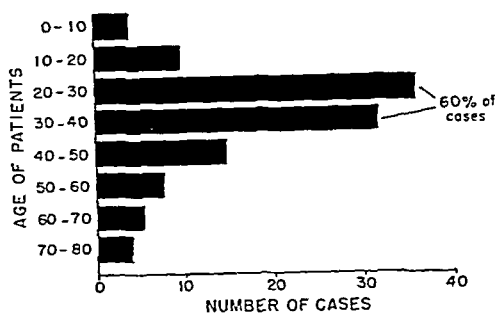


FIG. 1

TABLE 1. *Presenting symptoms*

|                          | CASES |
|--------------------------|-------|
| Enlarged testicle.....   | 93    |
| Pain in the testis.....  | 12    |
| Pain in the abdomen..... | 4     |
| Back pain.....           | 3     |
| Loss of appetite.....    | 2     |
| Pain in the groin.....   | 2     |
| Dragging sensation.....  | 1     |
| Cough and sputum.....    | 1     |
| Mass in the neck.....    | 1     |
| Weak and tired.....      | 1     |
| Weight loss.....         | 1     |
| Jaundice.....            | 1     |

TABLE 2. *Sites of metastases*

|                              | CASES |
|------------------------------|-------|
| Retroperitoneal.....         | 73    |
| Pulmonary.....               | 40    |
| Cervical lymph nodes.....    | 12    |
| Mediastinal lymph nodes..... | 6     |
| Spine.....                   | 6     |
| Pelvic bones.....            | 4     |
| Peritoneal cavity.....       | 3     |
| Ribs.....                    | 2     |
| Liver.....                   | 2     |
| Brain.....                   | 2     |
| Meninges.....                | 1     |
| Adrenal.....                 | 1     |
| Scapula.....                 | 1     |
| Penis.....                   | 1     |
| Intra-ocular.....            | 1     |
| Diaphragm.....               | 1     |

In 31 cases of this series an Aschheim-Zondek determination was performed. Seventeen were positive and fourteen were negative. Therefore, in this group of

patients, the test was only slightly better than 50 per cent positive as a diagnostic aid.

In this series, the tumors were divided into the following groups: seminomas, adult teratomas, embryonal carcinomas, teratocarcinomas and chorio-epitheliomas. However, some of our cases were seen prior to the use of this classification and were reported as embryomas, which apparently was a general classification



FIG. 2. Cystogram showing tumor mass in pelvis encroaching on bladder producing a deformity commonly seen in female patients from enlarged uterus.



FIG. 3. *A*, excretory urogram showing mass of metastatic tissue obstructing right ureter and producing nonfunctioning right kidney. *B*, retrograde pyelograms on same case proving presence of right kidney.

of all testicular tumors. The accompanying table lists the pathological types and the frequency with which they were seen (table 3).

The treatment of these tumors has consisted of orchiectomy and radiation therapy. Seminomas have responded best to this type of therapy. The remaining types of testicular neoplasms present a difficult problem in management, since they are not sensitive to deep x-ray therapy and orchiectomy invariably misses the metastatic malignant cells. In our series of cases, 107 had orchiectomies and



FIG. 4. Retrograde pyelograms revealing retroperitoneal metastasis from testicular neoplasm that produced displacement of right ureter.

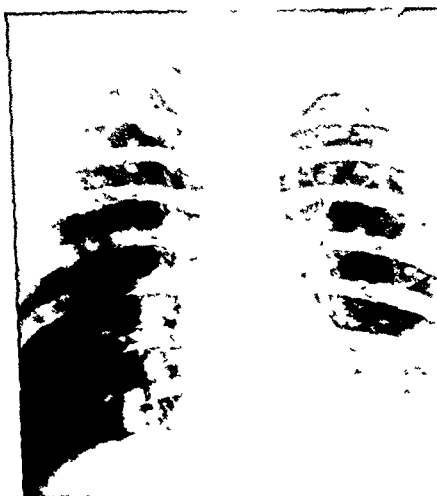


FIG. 5. Chest x-ray showing metastasis to lung fields from testicular neoplasm

97 cases had postoperative deep x-ray therapy which was delivered to the abdomen, lungs, neck and other areas, depending on the site of metastasis. The average dose delivered to the abdomen was 7,000 to 10,000 roentgens, while the average dose to the chest was 2,000 to 5,000 roentgens. Nine cases with retro-

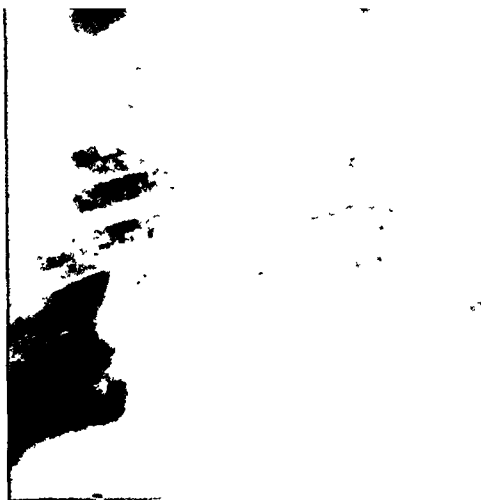


FIG. 6. Chest x-ray showing metastasis to mediastinum, lung fields and lymph nodes of neck from a testicular neoplasm.



FIG. 7. X-ray of shoulder girdle revealing metastatic lesion of testicular neoplasm to scapula.

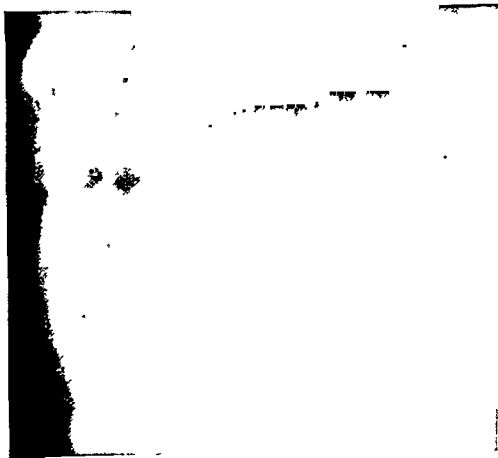


FIG. 8. X-ray of spine showing metastatic lesion involving posterior portion of twelfth thoracic vertebra.



FIG. 9. Cystogram showing metastasis from testicular neoplasm involving bones of pelvis.

TABLE 3. *Pathological types and frequency encountered*

|                     | CASES | PER CENT |
|---------------------|-------|----------|
| Seminoma .          | 39    | 40.2     |
| Embryonal carcinoma | 17    | 17.8     |
| Teratoma            | 16    | 16.4     |
| Embryoma            | 14    | 14.4     |
| Teratocarcinoma     | 9     | 9.2      |
| Chorio-epithelioma  | 1     | 1.03     |
| Mixed tumor         | 1     | 1.03     |

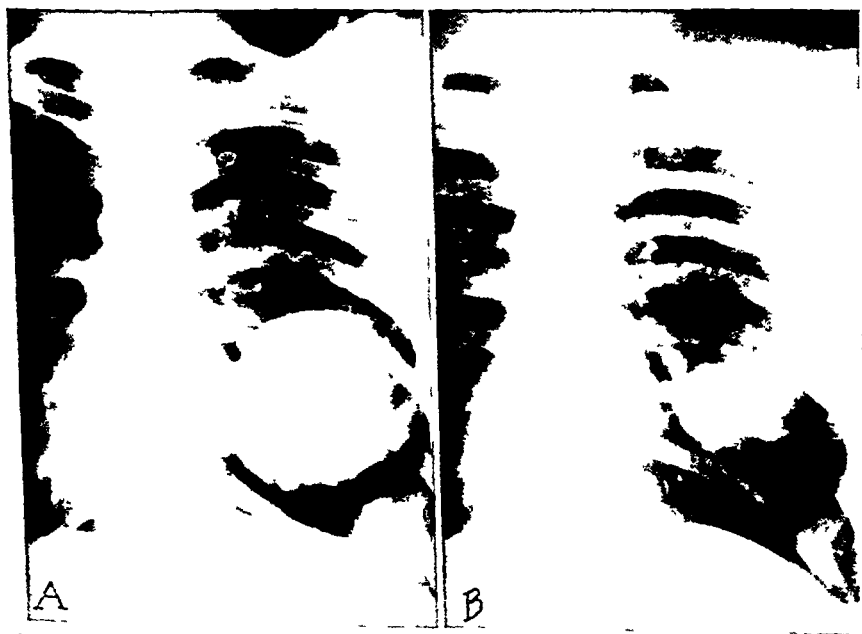


FIG. 10. A, chest x-ray prior to radiation therapy. B, chest x-ray following radiation therapy.

peritoneal metastasis or lung metastasis from a seminoma of the testis had marked regression in the size of metastatic mass following deep x-ray therapy (fig. 10). However, the majority of these again increased in size and failed to respond to a second course of roentgen therapy.

Follow-up information has been obtained on 106 patients. Thirty-seven of the series are still alive. The survival time is illustrated in table 4. At the end of 1 year, 21.7 per cent of the patients had expired and 50 per cent of the series failed to live beyond 3 years. There were 28 five-year survivals. Nineteen patients lived ten years or longer (table 5). Nine of the 37 living patients have metastases: retroperitoneal nodes, 4 cases; lungs, 3 cases; spine, 2 cases; and

TABLE 4. *Survival time, patients living, 37 cases*

|                   | CASES |
|-------------------|-------|
| 0-6 months .. ... | 1     |
| 7-12 months.. .   | 1     |
| 1-2 years         | 2     |
| 2-3 years         | 3     |
| 3-4 years         | 2     |
| 4-5 years         | 1     |
| 5-6 years         | 2     |
| 6-7 years         | 1     |
| 7-8 years         | 3     |
| 8-9 years         | 2     |
| 9-10 years        | 3     |
| 10-11 years       | 1     |
| 11-12 years       | 3     |
| 12-13 years       | 0     |
| 13-14 years       | 2     |
| 14-15 years       | 2     |
| 15-16 years       | 0     |
| 16-17 years       | 1     |
| 17-18 years       | 3     |
| 18-19 years       | 0     |
| 19-20 years ..    | 1     |
| 20-21 years       | 2     |
| 21-22 years       | 1     |

ribs, 1 case. All but two of the surviving patients with metastasis were cases of seminoma. The exceptions were an embryonal carcinoma alive 7 months after the diagnosis and a mixed tumor which has survived 16 months. The group of patients who responded best to our type of treatment have been the seminomas. In reviewing the survivals, it was interesting to see that despite the pathological diagnosis, if the patient came without demonstrable metastasis, he had a 70.8 per cent chance for five-year apparent cure (tables 6, 7, 8, 9, 10, 11).

Eighteen cases from this series illustrated the ease with which the diagnosis may be missed. Seven patients in this series were treated for a period of several weeks to three months for acute epididymitis before the diagnosis of a testicular tumor was made. In 5 cases the family physician had performed repeated tap-

TABLE 5. *Survival time of active series*

| TIME EXPIRED | CASES | PER CENT               |
|--------------|-------|------------------------|
| 0-6 months   | 7     | 93.4                   |
| 6-12 months  | 16    | 78.3                   |
| 1-2 years    | 16    | 63.2                   |
| 2-3 years    | 16    | 48.1                   |
| 3-4 years    | 9     | 39.6                   |
| 4-5 years    | 4     | 35.8 (5 yr. survival)  |
| 5-6 years    | 3     | 33.0                   |
| 6-7 years    | 1     | 32.0                   |
| 7-8 years    | 6     | 26.4                   |
| 8-9 years    | 4     | 22.7                   |
| 9-10 years   | 3     | 18.8 (10 yr. survival) |
| 10-11 years  | 2     | 17.9                   |
| 11-12 years  | 4     | 14.1                   |
| 12-13 years  | 1     | 13.2                   |
| 13-14 years  | 2     | 11.3                   |
| 14-15 years  | 2     | 9.4 (15 yr. survival)  |
| 15-16 years  | 0     | 9.4                    |
| 16-17 years  | 1     | 8.4                    |
| 17-18 years  | 3     | 6.7                    |
| 18-19 years  | 0     | 6.7                    |
| 19-20 years  | 2     | 3.8 (20 yr. survival)  |
| 20-21 years  | 2     | 1.8                    |

TABLE 6. *Seminoma*

|                               | ALIVE            | 5 YRS | 10 YRS | 15 YRS | 20 YRS |
|-------------------------------|------------------|-------|--------|--------|--------|
| With metastasis (21 cases)    | 5 cases (23.8%)  | 47.6% | 28.5%  | 4.76%  |        |
| Without metastasis (18 cases) | 17 cases (94.4%) | 88.8% | 77.7%  | 61.1%  | 22.2%  |
| Total (39 cases)              | 22 cases (56.4%) | 66.6% | 51.2%  | 30.7%  |        |

TABLE 7. *Embryonal carcinoma*

|                              | ALIVE           | 1 YR. | 2 YRS. | 3 YRS | 15 YRS. |
|------------------------------|-----------------|-------|--------|-------|---------|
| With metastasis (14 cases)   | 1 case (7.14%)  | 50%   | 21.4%  | 0%    | 0%      |
| Without metastasis (3 cases) | 3 cases (100%)  | 100%  | 66%    | 66%   | 33.3%   |
| Total (17 cases)             | 4 cases (23.5%) | 58.8% | 29.4%  | 11.7% | 5.8%    |

pings of hydroceles. When these patients failed to respond, bimanual palpation of the scrotum following the tappings revealed an enlargement of the testicle and a diagnosis of testicular neoplasm was finally established. Two patients were treated as cases of injury to the scrotum; in four additional cases the pa-



peritoneal metastasis or lung metastasis from a seminoma of the testis had marked regression in the size of metastatic mass following deep x-ray therapy (fig. 10). However, the majority of these again increased in size and failed to respond to a second course of roentgen therapy.

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TABLE 4. *Survival time, patients living; 37 cases*

|                 | CASES |
|-----------------|-------|
| 0-6 months..... | 1     |
| 7-12 months.... | 1     |
| 1-2 years       | 2     |
| 2-3 years       | 3     |
| 3-4 years       | 2     |
| 4-5 years       | 1     |
| 5-6 years       | 2     |
| 6-7 years       | 1     |
| 7-8 years       | 3     |
| 8-9 years       | 2     |
| 9-10 years      | 3     |
| 10-11 years     | 1     |
| 11-12 years     | 3     |
| 12-13 years     | 0     |
| 13-14 years     | 2     |
| 14-15 years     | 2     |
| 15-16 years     | 0     |
| 16-17 years     | 1     |
| 17-18 years     | 3     |
| 18-19 years     | 0     |
| 19-20 years     | 1     |
| 20-21 years     | 2     |
| 21-22 years     | 1     |

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Eighteen cases from this series illustrated the ease with which the diagnosis may be missed. Seven patients in this series were treated for a period of several weeks to three months for acute epididymitis before the diagnosis of a testicular tumor was made. In 5 cases the family physician had performed repeated tap-

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| 1-2 years    | 16    | 63.2                   |
| 2-3 years    | 16    | 48.1                   |
| 3-4 years    | 9     | 39.6                   |
| 4-5 years    | 4     | 35.8 (5 yr. survival)  |
| 5-6 years    | 3     | 33.0                   |
| 6-7 years    | 1     | 32.0                   |
| 7-8 years    | 6     | 26.4                   |
| 8-9 years    | 4     | 22.7                   |
| 9-10 years   | 3     | 18.8 (10 yr. survival) |
| 10-11 years  | 2     | 17.9                   |
| 11-12 years  | 4     | 14.1                   |
| 12-13 years  | 1     | 13.2                   |
| 13-14 years  | 2     | 11.3                   |
| 14-15 years  | 2     | 9.4 (15 yr survival)   |
| 15-16 years  | 0     | 9.4                    |
| 16-17 years  | 1     | 8.4                    |
| 17-18 years  | 3     | 6.7                    |
| 18-19 years  | 0     | 6.7                    |
| 19-20 years  | 2     | 3.8 (20 yr. survival)  |
| 20-21 years  | 2     | 1.8                    |

TABLE 6. *Seminoma*

|                               | ALIVE            | 3 YRS | 5 YRS | 10 YRS | 15 YRS | 20 YRS |
|-------------------------------|------------------|-------|-------|--------|--------|--------|
| With metastasis (21 cases)    | 5 cases (23.8%)  | 47.6% | 28.5% | 4.76%  |        |        |
| Without metastasis (18 cases) | 17 cases (94.4%) | 88.8% | 77.7% | 61.1%  | 22.2%  | 11.1%  |
| Total (39 cases)              | 22 cases (56.4%) | 66.6% | 51.2% | 30.7%  |        |        |

TABLE 7. *Embryonal carcinoma*

|                              | ALIVE           | 1 YR  | 2 YRS | 3 YRS | 15 YRS. |
|------------------------------|-----------------|-------|-------|-------|---------|
| With metastasis (14 cases)   | 1 case (7.14%)  | 50%   | 21.4% | 0%    | 0%      |
| Without metastasis (3 cases) | 3 cases (100%)  | 100%  | 66%   | 66%   | 33.3%   |
| Total (17 cases)             | 4 cases (23.5%) | 58.8% | 29.4% | 11.7% | 5.8%    |

pings of hydroceles. When these patients failed to respond, bimanual palpation of the scrotum following the tappings revealed an enlargement of the testicle and a diagnosis of testicular neoplasm was finally established. Two patients were treated as cases of injury to the scrotum; in four additional cases the pa-

tients were treated as cases of renal colic, lung tumor, appendicitis and hepatitis. From these 18 cases the following are reported as interesting and unusual.

TABLE 8. *Teratoma*

|                              | ALIVE           | 1 YR. | 5 YRS | 10 YRS | 15 YRS |
|------------------------------|-----------------|-------|-------|--------|--------|
| With metastasis (8 cases)    | 0 cases (0%)    | 50%   | 12.5% | 0%     | 0%     |
| Without metastasis (6 cases) | 6 cases (100%)  | 100%  | 100%  | 50%    | 33%    |
| Total (14 cases)             | 6 cases (42.8%) | 71.4% | 50%   | 21.4%  | 14.2%  |

TABLE 9. *Embryoma*

|                             | ALIVE         | 1 YR. | 3 YRS. | 5 YRS | 10 YRS |
|-----------------------------|---------------|-------|--------|-------|--------|
| With metastasis (12 cases)  | 0 cases (0%)  | 91.6% | 50%    | 25%   | 8.3%   |
| Without metastasis (1 case) | 1 case (100%) | 100%  | 100%   | 100%  | 0%     |
| Total (13 cases)            | 1 case (8.3%) | 92.3% | 53.8%  | 30.7% | 8.3%   |

TABLE 10. *Teratocarcinoma*

|                             | ALIVE          | 1 YR. | 5 YRS | 10 YRS |
|-----------------------------|----------------|-------|-------|--------|
| With metastasis (10 cases)  | 0 cases (0%)   | 50%   | 10%   | 0%     |
| Without metastasis (1 case) | 1 case (100%)  | 100%  | 0%    | 0%     |
| Total (11 cases)            | 1 case (9.09%) | 55.5% | 9.09% | 0%     |

TABLE 11. *Five year survival of patients without demonstrable metastasis*

|                     | CASES | ALIVE 5 YRS |
|---------------------|-------|-------------|
| Seminomas           | 18    | 13          |
| Embryonal carcinoma | 3     | 2           |
| Teratoma            | 1     | 1           |
| Embryoma            | 1     | 1           |
| Teratocarcinoma     | 1     | 0           |
| Total               | 24    | 17 (70.8%)  |

## CASE REPORTS

*Case 1.* B. J., No. 49-7781, was a 20 year old white man who was admitted with the chief complaint of pain in his right hip and a weight loss of 32 pounds. He had been well until January 1949, when he noticed a tired sluggish feeling and a dull annoying soreness above the right iliac crest. Two months later, a dull, vague, fleeting pain developed in his back, 5 inches below the right scapula. His skin became yellow and the stools clay colored. An exploratory laparotomy was performed and a pancreatic cyst was drained. Postoperatively, nontender enlarged cervical lymph nodes developed on the left side. When he failed to respond to treatment, he was referred to the University Hospitals.

The patient was a chronically ill, listless male with evidence of weight loss. There were several firm, rubbery, discrete, movable, non-tender lymph nodes in the neck. These nodes produced visible swelling at the base of the neck in the supraclavicular region, particularly on the left side. The heart revealed a palpable systolic thrill with regular rate and rhythm, and a harsh crescendo systolic murmur which was heard best at the fourth intercostal space at the left sternal border. The abdominal examination revealed a well healed recent operative scar in the right upper quadrant. A palpable nodular mass 10 by 5 cm. extended from the mid epigastrium downward and laterally to the right of the umbilicus. It was nodular, firm, and rubbery in consistency. The left testicle was slightly enlarged.

Pathological report of tissue removed by biopsy from cervical lymph nodes revealed a poorly differentiated metastatic adenocarcinoma. X-rays of the chest and pelvis were negative. Anteroposterior and lateral views of the lumbosacral spine revealed a marked scoliosis in the upper lumbar region with a convexity to the left. Excretory urograms revealed intrinsically normal kidneys with displacement laterally of the lower pole of each kidney and the proximal half of each ureter by a retroperitoneal mass. An Aschheim-Zondek test was positive and the final impression was that the patient had a testicular tumor. A left orchiectomy was performed and pathologically the tissue revealed a chorioepithelioma. He was treated by x-ray therapy, 300 roentgens daily, to anterior and posterior ports for 3 to 5 days. The patient at the present time is still living.

*Case 2.* I. H., No. 41-116, was a 31 year old white man who was admitted with a chief complaint of paralysis of the legs and pain in the back. It began with numbness in his right knee, which increased until it involved the entire leg. Later the numbness appeared in the left thigh and progressed down to the left foot. At the same time weakness appeared in both legs, but the patient continued up and around until 2 days prior to admission when he became completely paralyzed. The night prior to admission he went into complete urinary retention.

Physical examination revealed a well-developed, well nourished white man in no acute distress, but who was unable to move his legs. The bladder was distended to the umbilicus, and tenderness was present over the fifth and sixth dorsal vertebrae. Examination of the genitalia revealed a hard, non-tender, egg-sized swelling of the right testicle. There was a complete loss of muscle power below the umbilicus; 900 cc of residual urine was found. Excretory urograms showed slight hydronephrosis on each side. There were a few red blood cells and an occasional white blood cell in the urine. A cystometrogram revealed a flaccid neurogenic bladder. An Aschheim-Zondek test was positive. X-rays of the spine showed a destructive lesion, metastatic in origin, involving the fifth and sixth dorsal lumbar vertebrae with a soft tissue mass on the lateral side of the vertebrae. A right orchiectomy was performed and the pathological report revealed a seminoma of the testicle. A suprapubic cystostomy was performed, and 1,200 roentgens were delivered to the upper dorsal spine. He was discharged from the hospital and expired 1 month later.

*Case 3.* D. J., No. 38-22122, was a 31 year old white man who was admitted with a chief complaint of a swollen testicle. Two and a half months prior to

admission he noticed soreness in the right testicle. Six weeks prior to admission the right scrotal contents began to swell and became very painful.

Physical examination was normal except for the genitalia, which revealed the right testicle and scrotal contents to be enlarged, tense, red and tender. The impression was that the patient had a right epididymitis. Laboratory studies were negative except for a white blood count of 14,450. Excretory urograms were normal. X-rays of the lungs showed a healthy chest. The patient was treated for acute epididymitis and discharged.

He returned to the hospital unimproved and had lost weight. Impression on this admission was that the patient had a testicular tumor. The Aschheim-Zondek test was negative. On August 18, 1938, a right orchiectomy was performed. A cross section of the testicle showed the entire organ to be involved in a neoplastic process. The pathological report was an embryoma of the testicle. He was known to be alive on October 20, 1950.

Case 4. L. B., No. 47-5082, was a 17 year old white man who was admitted with the chief complaints of pain in his abdomen, constipation, nausea and vomiting. Four days prior to admission the patient thought he was constipated and administered an enema with good results. The cramping pain in the left abdomen moved to the midabdomen and the region of the umbilicus. The day prior to admission the patient began to localize the pain in the region of the right lower quadrant. Another enema produced five to six mushy medium brown stools. The abdomen then became hard and remained so until admission.

Physical examination revealed a well developed, well nourished white man who appeared to be in considerable pain. The upper abdomen was tympanitic and below the umbilicus it was distended, hard and dull to percussion. Examination of the genitalia revealed the left testicle palpable in the inguinal canal. Rectal examination revealed a large bulging, firm, non-tender mass above the prostate. Excretory urograms revealed bilateral function with caliectasis and hydro-ureter on the left side. A mass which obliterated the psoas shadows could be outlined from the symphysis to the umbilicus. An x-ray of the chest revealed no evidence of neoplastic disease. An Aschheim-Zondek test was negative. The colon series showed incomplete filling of the colon.

The patient had dyspnea and abdominal distention. The mass appeared to be enlarging. Therefore, on May 14, 1947, an exploratory laparotomy was done. When the peritoneum was opened, a large, fungating, soft, friable, vascular mass bulged through the peritoneum. Frozen sections showed a very cellular neoplasm which was possibly a lymphoma. The patient remained in shock during the procedure and expired about 13 hours later.

An autopsy revealed an undescended, soft, yellow testicle in the region of the left internal inguinal ring. Microscopically it was composed of large, round, oval neoplastic cells. The left iliac lymph nodes were involved with metastatic tumor. The entire peritoneal cavity was covered with a soft, yellow, necrotic, neoplastic tissue and contained 300 cc of a bloody fluid. The liver weighed 3200 gm., and numerous small neoplastic nodules were present throughout its substance. Metastases were also noted in the perineal, pancreatic, gastro, splenic, subdiaphragmatic, mediastinal, and retroperitoneal lymph nodes. Death was

attributed to widespread extension and metastasis of a seminomatous neoplasm of the left undescended testicle.

Case 5. E. S., No. 41-1375, was an 18 year old white man who was admitted with the chief complaint of enlargement of the right testicle. At times he had been nauseated and complained of an infrequent pain in the right costovertebral angle.

Physical examination revealed a well developed white man who did not appear acutely ill. The eyes reacted to light and accommodation, and there were normal extraocular movements. Examination of the genitalia revealed the right testicle to be the size of a hen's egg, hard and irregular, but non-tender. A chest x-ray revealed a shadow of increased density about 1.5 cm. in diameter on the right, beneath the tenth rib posteriorly. Excretory urograms were normal; an Aschheim-Zondek test was positive. A right orchiectomy was performed. Postoperatively the patient received x-ray therapy which consisted of 4,000 roentgens to each kidney pedicle, 2,000 to each groin, and 8,000 to the chest. Microscopic sections showed replacement of the testicular tissue with a large, pale, neoplastic



FIG. 11. A, metastasis to left orbit from neoplasm of testis. B, pronounced improvement in metastasis to left orbit following x-ray therapy.

cell. The impression was embryoma of the testicle. Following x-ray therapy the patient was discharged.

After 1 week the patient returned to the hospital because of pain in his left eye. The eye became swollen and he lost all vision (fig. 11, A). Examination revealed marked edema of the bulbar conjunctiva. The pupil was dilated to about 5 mm. and did not react to light, but showed a little constriction to accommodation. The temporal half of the vitreous body was filled with a gray opaque mass. The retina was noted to be detached in all except the nasal  $\frac{1}{3}$  of the fundus. Tension was elevated to palpation and was high with the tenometer.

X-ray therapy consisting of 2,000 roentgens to the left lateral orbit was administered. There was marked regression of the swelling of the eye and diminished pain (fig. 11, B). Repeat chest x-ray at this time showed extensive miliary metastases involving both lungs; an x-ray of the left orbit revealed a tumor which was producing erosion of the bony roof (fig. 12). He was discharged, but was readmitted 2 months later in a terminal state. The final diagnosis was a testicular tumor with metastases to the retroperitoneal lymph nodes, the lungs, the cervical lymph nodes, and to the left orbit.

*Case 6.* E. K., No. 41-7187, was a 33 year old white man who was admitted with the chief complaint of cough for the past 9 months. When it became progressively worse, a chest x-ray was performed which was interpreted as revealing a lung tumor. While at work, he fell, struck his chest and fractured several ribs. An irritating cough continued and became productive of foul, yellowish sputum. One week prior to admission night sweats and dyspnea developed; he coughed up one cup of sputum daily. On the day of admission, hemoptysis developed.

Physical examination revealed a pale, thin, dyspneic, chronically ill white man whose skin was hot and moist. The trachea was deviated to the right side. A congenital concavity of the chest was present and respiratory motions of the thoracic cage were absent on the left side. Percussion of the left side of the chest was dull and flat. Breath sounds over the same area were bronchial. Examination



FIG. 12. X-ray of skull and orbits showing destruction of bony orbit and tumor mass filling orbit on left side.

of the abdomen revealed the liver to be palpable one finger breadth below the costal cage, but no other organs or masses were palpable. A hard, non-tender mass in the right scrotum involved the testicle and did not transmit light.

Shortly after admission the patient became dyspneic and had a spasm of coughing. He perspired profusely, but was not cyanotic. Nasal oxygen produced some relief. His temperature rose to 102F. An x-ray of the chest revealed atelectasis of the left lung. An Aschheim-Zondek test was negative. Sputum cultures revealed pneumococcus type VIII plus the normal flora. A right orchiectomy was performed and the cut section of the testicle revealed the substance to be replaced by a friable, yellow tissue. Pathological report was an embryonal carcinoma. He had pain in the left shoulder, chills, fever and vomiting. At post-mortem examination, the left lung was filled with a soft neoplasm. The lung was firmly adherent to the parietal pleura, and there were marked areas of degenera-

tion and necrosis with two areas of abscess in the lower lobe. The mediastinum was solid with a soft, yellow tumor mass and the hilar nodes of both lungs were enlarged. There was also metastatic involvement of the retroperitoneal lymph nodes.

### CONCLUSIONS

Erroneous conclusions may be drawn by comparing the percentage of cures in one series with the percentage of cures in another. Many factors influence the statistics of a series of cases, and unless these are known or are the same in both groups false impressions will be established. It is a mistake to try to treat all testicular tumors in the same manner. Even within the same pathological groupings, there are pronounced differences in the rate of growth, degree of metastasis, and the type of response to the various methods of treatment. Therefore, each case must be individually evaluated and treated.

L. G. Lewis reported a series of 169 patients who were treated by radical surgical removal of the testicle and the retroperitoneal lymph nodes. These cases were seen over a period of 4 years beginning in May 1942. At the time the report was made in 1948, 24 per cent of the patients had expired. He had no operative mortality, but 34 per cent of the group had metastases to the nodes at the time of operation and 29 per cent of these, or 10 per cent of the entire group, were considered inoperable. Unfortunately, sufficient time had not elapsed to adequately evaluate the results of the treatment. His results at that early date with radical surgery were markedly better than the group treated by simple orchiectomy. However, the cases treated by conservative procedures were those with metastasis and a little further advanced in the course of the disease. At the same time, some of the patients subjected to radical surgery may have survived the same length of time with only the simple orchiectomy. Therefore, a longer period of time must elapse before definite conclusions can be reached with regards to the value of radical surgery. If the cases in this series who had not been seen over a long enough period of time are eliminated from the statistics, we have 100 per cent survival for seminomas without metastasis over a 10 year period. This would seem to indicate that in this group, simple orchiectomy and postoperative x-ray therapy has been satisfactory.

Unfortunately the other pathological groups have not responded as well to this method of therapy. In addition, the majority of these other groups had demonstrable metastasis and, therefore, were not satisfactory for radical surgery. There were 11 cases in our series that could possibly have fulfilled the prerequisites for radical surgical procedure. Therefore, we believe that there is an indication for radical removal of lymph nodes, and that this falls in the groups who are not radiosensitive and who do not have metastases. We also are of the opinion that simple orchiectomy and postoperative x-ray therapy in the case of seminoma will probably produce as good a result as radical surgical procedures plus radiation.

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The numerous etiologic factors responsible for the syndrome of precocious puberty are listed as follows in order of frequency.

*Male*

1. Constitutional (idiopathic)
2. Intracranial
3. Adrenal cortex
  - a. Hyperplasia
  - b. Tumor
4. Testicular

*Female (Idiopathic)*

1. Constitutional (idiopathic)
2. Ovarian
3. Albright's syndrome
4. Intracranial

*Female (Etiological)*

1. Adrenal cortex
  - a. Hyperplasia, prenatal
  - b. Tumor
  - c. Hyperplasia, postnatal

## CONSTITUTIONAL (IDIOPATHIC) TYPE

By far and away the most frequent type of precocious puberty is that known as constitutional or idiopathic. An isosexual complete maturation develops in both sexes for which no discernible lesion can be discovered. The syndrome may become evident as early as the first year, nonetheless these children live to adult life and do not suffer premature senility.

The clinical picture is that of somatic overgrowth, large genitals and presence of sexual hair. Bone age is advanced as is tooth age although not correspondingly so. Intelligence and psychosexual development are ordinarily that of the chronologic age. The gonad is mature and ovulatory menstruation occurs in the female and spermatogenesis in the male. 17-Ketosteroid, estrogen and androgen titres are within adolescent levels.

Some social maladjustment may develop in boys with this syndrome because of the disproportion between the child's markedly advanced physical size and his mental level which is usually that of his proper age.

Sexual maturation of this type in females can lead to serious problems. Numerous pregnancies have been reported among these girls. Much publicity attended a recent such case of a Peruvian girl who was delivered by caesarian section of a 6 pound infant when she was 5½ years old.

*Case 1.* J. C. (423685) admitted to Mount Sinai Hospital May 1938, was a 7½ year old white boy with history of marked enlargement of the genitalia since the age of 1 year. Body size had grown rapidly and progressively to youthful proportions. Recently the child had demonstrated a marked heterosexual drive.

The patient had been born at term and weighed 7 pounds. Early growth and development were not remarkable. Three other siblings had died in childhood. Familial history was negative.

Examination revealed a well-proportioned male child approximately the size and weight of a 1½ year old boy. He was commensurately strong, active and alert. Dentition was normal for age. Complete neurologic examination resulted in normal findings. Heart and lungs were normal. Blood pressure, 100/70. No ab-

## PRECOCIOUS PUBERTY

JOSEPH M. SILAGY

*From the Urologic Service, the Mount Sinai Hospital, New York, N. Y.*

The syndrome of precocious puberty can be produced by a variety of etiologic factors. The urologist is frequently called upon to aid in the differential diagnosis and the treatment of these interesting patients. A review of the subject and a presentation of illustrative cases are therefore deemed of interest.

Part of the biologic uniqueness of man lies in a prolonged period following birth before sexual maturity develops. The onset of puberty is a variable phenomenon depending on genetic, racial, climatic, nutritional and other factors. The ninth or tenth year is accepted as the normal age of onset of puberty; somewhat later in the male. Sexual maturation which considerably antedates this time period must be regarded as precocious.

The normal progress and timing of sexual maturity is effected in a correlated and synchronized manner. It is believed that the hypothalamus is the center for sexual maturation and various vegetative functions. This area remains inhibited prior to the second decade of life; then, for reasons not completely understood, disinhibition occurs and the hypothalamus exerts its influence upon the anterior pituitary gland which in turn produces its hormones. The "tropic" hormones of the pituitary activate the "target glands," i.e., the adrenals, gonads, thyroid, etc. which in turn secrete hormones bringing about development and maturation of their respective end organs. The "target gland" hormones, when produced in proper quantity, also inhibit excessive pituitary function thus establishing a self-regulating endocrine mechanism.

When the entire integrated hormonal mechanism is set into motion, the result is an individual with well marked secondary sexual characteristics appropriate to his sex, and a mature gonad capable of producing gametes. This is known as isosexual complete maturation and is brought about normally at the time of adolescence, or it can be induced prematurely by some disorder arising at the level of the brain centers or of the anterior pituitary (constitutional or intracranial types).

A disorder in hormonal control arising at the level of the adrenal or of the gonad will result in an individual with well-marked secondary sexual characteristics of either the iso- or heterosexual type. The gonad, however, not having been stimulated by pituitary gonadotropins, retains its infantile state and is incapable of producing mature gametes (adrenal or gonadal types). This disproportion between the development of the testis or ovary and the secondary sexual characteristics is known as incomplete sexual maturation or "dissociated" virilization or feminization.

Presented at Dr. G. D. Oppenheimer's urologic conference October 23, 1951.  
Accepted for publication July 30, 1952.

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2. Intracranial
3. Adrenal cortex
  - a. Hyperplasia
  - b. Tumor
4. Testicular

*Female (Isosexual)*

1. Constitutional (idiopathic)
2. Ovarian
3. Albright's syndrome
4. Intracranial

*Female (Heterosexual)*

1. Adrenal cortex
  - a. Hyperplasia, prenatal
  - b. Tumor
  - c. Hyperplasia, postnatal

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The patient had been born at term and weighed 7 pounds. Early growth and development were not remarkable. Three other siblings had died in childhood. Familial history was negative.

Examination revealed a well-proportioned male child approximately the size and weight of a 14 year old boy. He was commensurately strong, active and alert. Dentition was normal for age. Complete neurologic examination resulted in normal findings. Heart and lungs were normal. Blood pressure, 100/70. No ab-

dominal masses or viscera were palpable. There was fine black hair on face, arms and legs, and abundant pubic hair. Penis and testes were of adult size; epididymides and vasa were normal. The prostate was of adult size and well delimited; the vesicles were not distended. Psychologic tests revealed a mental level at 6-7 years. The I.Q. was from 85 to 113 by various standards. Examination of seminal ejaculate revealed normal motile spermatazoa of mature configuration. Blood urea nitrogen and sugar determinations normal. Na = 143.8 miliequivalents, Cl = 107 miliequivalents. BMR: minus 26. X-rays of skull showed normal sella; no evidence of increased intracranial pressure. Bone age 12-13 years. Excretory urography showed a normal urinary tract. Perirenal insufflation showed normal adrenal shadows. Hormone studies (72 hour urine specimen) negative for gonadotropic hormone, estrogenic hormone 1,000 units/litre.

The child was not heard from again until 1945, when at the age of 15 he was sent to the N. Y. State Training School, an institution for juvenile delinquents. Health had remained good and there had been no evidence of intracranial or other disease.

Comment: This case may tentatively be classified as constitutional or idiopathic because of the isosexual complete precocious maturation without discernible lesion. The presence of normal spermatozoa in the ejaculate is confirmatory. However, the finding of an abnormally high urinary estrogen titre is not readily explicable. It suggests some type of adrenal cortical hyperfunction.

#### INTRACRANIAL TYPE

The syndrome of precocious puberty can be produced by a variety of intracranial lesions, the most common being tumors, cysts, hamartomas and inflammatory diseases. Effects are produced either by direct involvement of the hypothalamic areas or by means of the internal hydrocephalus resulting from the lesion. Tumors of the pineal gland have long been implicated as a cause of precocious puberty. The effects of these tumors, however, are not believed to be due to secretory activity, but to extension into the hypothalamus. Bing, Globus and Simon, in a study of 56 cases of pinealoma occurring in children under age of 15, reported sexual precocity in 21, almost all of whom were boys. In all 21 cases the tumor was not restricted to the pineal. Fifteen of the 21 showed a constellation of vegetative dysfunctions indicative of hypothalamic injury.

Some of the lesions, such as hamartomas and cysts, do not expand and their recognition may therefore be masked for a prolonged period.

The premature sexual maturation produced by organic intracranial disease is of the isosexual complete variety in both sexes.

As in the constitutional group, the normal hormonal mechanism is activated. The clinical picture therefore closely resembles the one previously described except that other evidences of hypothalamic dysfunction often co-exist, e.g. adiposity, sleep disturbances, non-infectious temperature and pulse elevations, etc. Focal neurologic signs of the brain lesion are likewise present, i. e. failure of upward gaze, Argyle-Robertson pupils, etc. and, at times, evidence of increased intra-cranial pressure. The titres of the 17-ketosteroids and sex hormones are within adolescent limits.

*Case 2.* S. S. (623484) admitted to Mount Sinai Hospital May 1951, was a 2 year old white boy with a history of rapidly increasing body size, large penis and pubic hair first noted at age of 8 months. Child had been born at term by cesarian section of normal parents. One sibling died in infancy; two other siblings were normal. The familial history was negative. Growth and development of the patient were not unusual until the age of 8 months, when large genitals were first observed. At 11 months of age, child was seen by me at another hospital where a workup failed to disclose any etiologic factor. Perirenal air insufflations were normal. Testicular biopsies revealed prepuberal testes showing slight activity of seminiferous tubules. Skull films and neurologic examinations were negative, but pneumo-encephalography was not performed.

The child continued to grow rapidly in size, acne of face appeared and voice deepened. He was admitted to The Mount Sinai Hospital at the age of 2.

Child was a typical infant hercules in size and configuration. Bone age was 7. All deciduous teeth were present. Penis and testes were both markedly and proportionately enlarged to almost adult size (fig. 1). Pubic hair was present. General physical examination was otherwise normal. Blood Pressure. 105/55



FIG. 1. Case S. S. Complete isosexual precocious puberty in a 2-year old white boy caused by prepontine brain tumor. Compare with figure 4.

Neurologic examination was normal. The electro-encephalogram was normal. Testicular biopsies showed spermatocytogenesis with focal areas of complete spermatogenesis (fig. 2). 17-Ketosteroids: 1.26 mg./24 hrs. Other laboratory findings were within normal limits. Behavior and intelligence were judged normal for age.

Pneumo-encephalogram showed the cisterna interpeduncularis widened and pushed upwards. It was almost completely filled by a mass extending from the anterior surface of pons to the clivus. The tumor was considered surgically inaccessible. The child was referred for radiation therapy.

Comment: Isosexual, complete precocious puberty caused by deep-seated prepontine tumor. Testicular biopsies at age of 11 months showed slight activity of seminiferous tubules and normal spermatogenesis at age 2 years.

#### ALBRIGHT'S SYNDROME

Albright's syndrome, although incompletely understood, should probably be included in the organic intracranial group. The full syndrome consists of isosexual complete precocity, areas of skin pigmentation and polyostotic fibrous dysplasia. Eighteen of the 19 reported cases were in girls. Albright suggests

that there might be a congenital defect of the hypothalamus leading to stimulation of the pituitary and release of gonadotropins.

#### GONADAL TYPE

Precocious puberty can result from gonadal tumors that produce an excess of sex hormones. The secondary sexual characteristics may be strikingly matured, but the nontumorous gonad, in the absence of activation by pituitary gonadotropins, remains infantile. This situation, as discussed before, constitutes isosexual maturation of the incomplete variety.

Hormone secreting tumors of the ovary may be either malignant such as teratoid embryomas and chorio-epitheliomas; or benign, as is usually the case with granulosa cell tumors. The signs of premature sexual development are

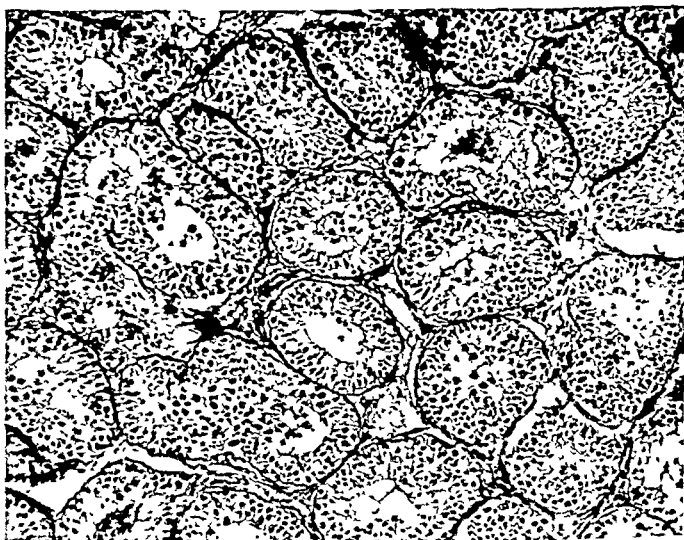


FIG. 2. Case S. S. Testicular biopsy from 2-year old boy showing spermatocytogenesis and focal areas of complete spermatogenesis.

associated with progressive cachexia and early death when the syndrome is produced by malignant new growths.

Granulosa cell tumors secrete large quantities of estrogens and are most often palpable by abdominal examination. Extreme feminization is the rule. Vaginal bleeding may occur in these cases but is not true menstruation, for ovulation does not take place and vaginal smears fail to show any progestational changes. Surgical removal of these neoplasms is followed by recession of the abnormal feminization.

Masculinizing tumors of the ovary have not been reported as a cause of precocious puberty, the youngest case of arrhenoblastoma having been over 15 years of age.

Adenoma or extensive hyperplasia of the interstitial cells of the testicle may bring about premature sexual development by virtue of excessive androgen secretion. The tumor bearing testis is usually enlarged; the other shows no changes

or may be atrophic. Moderate regression of the syndrome occurs after surgery. These cases are rare, only nine being recorded in a review of the subject by Melicow.

#### ADRENAL TYPE

Hyperfunction of the adrenal cortex caused either by tumor or hyperplasia can produce the syndrome of precocious puberty. The manifestations of the increased production of adrenal androgens in these cases depend upon the sex of the individual, and upon whether the hormonal dysfunction began in utero before complete differentiation of the sexual organs, or in the postnatal life:

*Manifestations of adrenal cortical hyperfunction according to sex and time of onset*

| ONSET         | LESION               | RESULTING ABNORMALITY              |                                            |
|---------------|----------------------|------------------------------------|--------------------------------------------|
|               |                      | Female                             | Male                                       |
| A. Congenital | Hyperplasia          | Pseudohermaphroditism              | Isosexual incomplete precocious maturation |
| B. Postnatal  | Tumor or hyperplasia | Heterosexual precocious maturation | Same (before puberty)                      |

#### CONGENITAL ADRENAL CORTICAL HYPERPLASIA IN FEMALES

This is the most common adrenal disorder in childhood and is often familial. Evidences of excessive production of androgen are present from early infancy on. A characteristic pseudohermaphroditism is evident at birth. The clitoris is hypertrophied and resembles a hypospadiac penis with absent spongiosum and marked chordee. The labia majora are present and between them is a shallow trough lined with mucous membrane which represents a persistent urogenital sinus. It is possible by urethroscopic examination of this sinus to demonstrate the urethra running anteriorly to the bladder and a communication posteriorly into the vagina. This abnormality suggests that the excessive androgens must have had their influence before the fifth month of intra-uterine life, thus preventing the differentiation of the müllerian duct derivatives and the establishment of normal urethral and vaginal relationships that ordinarily take place between the 60 and 170 mm. stage of the embryo.

As the child grows older, the clitoris increases in size, somatic growth and muscular development become far advanced, pubic and body hair appear early, acne becomes evident, the voice deepens, and a masculine aspect is assumed. The 17-ketosteroid excretion is considerably increased in relation to the patient's age.

Cases of congenital adrenal cortical hyperplasia can be differentiated from those in whom adrenal cortical hyperfunction develops postnatally. In the latter cases, virilization occurs after differentiation of the sexual organs has been completed and the urethra and vagina therefore show normal relationships. The external genitalia of some cases of intersex may be indistinguishable from those of congenital adrenal cortical hyperplasia, but muscular and somatic overgrowth is not present in the intersex and their 17-ketosteroid excretion is normal.



Therapy for congenital adrenal cortical hyperplasia has until recently been surgical. H. H. Young advocated and practiced bilateral sub-total adrenal resection and reported some improvement in his patients. This rather formidable procedure was not widely accepted. Recently, L. Wilkins reported beneficial effects from the use of cortisone. The use of this hormone results in a prompt drop in the excretion of the 17-ketosteroids and progressive virilization may thus be restrained. Plastic procedures are necessary, however, to correct the urethral and vaginal deformity.

*Case 3.* L. O. (631375), admitted to The Mount Sinai Hospital July 1951, was a 5-year old white female with the history of a large clitoris at birth, and recent rapidly increasing body size and presence of pubic hair.

The patient was the first born child of normal parents. She had been born at term weighing 7 pounds, 2 ounces. The mother noted that clitoris was enlarged at birth. Development and growth were otherwise normal until the age of 2 when large body size and growth of pubic hair became evident. At the age of 3 the child was taken to another hospital where complete workup was done and diagnosis



FIG. 3. Case L. O. Five-year old white girl showing characteristic pseudohermaphroditic appearance resulting from congenital cortical hyperplasia.

of congenital adrenal cortical hyperplasia was made. 17-Ketosteroid excretion at that time was 7.8 mg./litre.

The child continued to grow and developed great strength and size. There were frequent attacks of pimples on face. The breasts did not enlarge and no vaginal bleeding occurred. Behavior was that of a normal girl.

Physical examination revealed a large child with masculinized body contours and presence of pubic hair. Acne of the face was present. The clitoris was a penis-like organ of large size with retractable prepuce. The organ was bound down ventrally and the spongiosum was absent (fig. 3). A vulvar trough of mucous membrane was evident completing the picture of a typical female pseudohermaphrodite. No testes could be made out and no prostate was evident to rectal touch. No abdominal masses or viscera were palpable. The voice was high-pitched. Intelligence was normal for age and behavior was quite feminine. Routine laboratory examinations were within normal limits. The bone age was 10 years. The excretory urograms showed normal upper tracts. No evident suprarenal masses.

Panendoscopy revealed a normal urethral channel leading upwards to bladder from anterior aspect of vulvar opening. Upon withdrawing the instrument, a communication posteriorly was noted which led into a long tube lined by mucous membrane. Hippuran injected into this tube outlined a normal vagina.

17-Ketosteroid excretion, 21.66 mg./litre. 11 Oxysteroids, 0.49 mg./litre. The patient was given a course of cortisone therapy, 25 mg. by mouth t.i.d. and there was a prompt response with 17-ketosteroids falling to normal limits.

Comment: Case of precocious sexual maturation of hetero-sexual type with pseudohermaphroditism typical of congenital adrenal cortical hyperplasia. Prompt drop in 17-ketosteroid excretion with the use of cortisone.

#### ADRENAL HYPERPLASIA AND TUMOR IN MALES

Hyperfunction of the adrenal cortex, the result of either hyperplasia or tumor, produces an incomplete precocious sexual maturation in both sexes. Adrenal cortical hyperplasia has a high familial incidence; several siblings may be affected. Because of the co-existence of evidences of adrenal insufficiency in this condition not a few die in infancy. Those who survive go on to remarkable somatic and genital overgrowth. The clinical aspect of cortical hyperplasia and tumor in males is alike. The patients grow rapidly and are quite muscular. Penis and prostate enlarge almost to adult size. The testes, however, remain infantile. Testicular biopsies show some tubular development but the Leydig cells are not activated and spermatogenesis does not occur. The picture of large penis and small testes constitutes dissociated virilization and is an important diagnostic consideration. In both tumor and hyperplasia, the excretion of the 17-ketosteroids is markedly increased; the beta fraction is said to be particularly high in cases of tumor. Perirenal air insufflation and laminography will often outline adrenal tumors. The method recently introduced by Ruiz Rivas whereby air introduced into the presacral space readily ascends the lumbar gutters to outline both perirenal areas has made the procedure both easy and safe. Frequently, however, surgical exploration must be carried out to differentiate between adrenal cortical tumor and hyperplasia. The treatment of tumor is, of course, surgical extirpation.

Bilateral subtotal adrenal resection has been advised for diffuse cortical hyperplasia. Before this is done, it would be advisable to give cortisone therapy for it may well reduce androgenic hyperfunction in boys as well as in girls.

Case 4. C. R. (626852), admitted to The Mount Sinai Hospital June 1951, was a 2½ year old Negro boy with history of rapid growth in size, and large genitals. The large penis, which had been noted at age of 6 months, gradually increased in size as did bodily stature. Pubic hair appeared at 2 years and the voice deepened. The patient was the second of three children; other two siblings normal. Child had been well except for convulsive episodes which were associated with fever and tonsillitis. The familial history was negative.

Examination showed a strikingly developed boy with well-proportioned herculean habitus. He was alert and did not appear ill. Fine pubic hair present; no axillary hair. Penis was enlarged to almost adult size; the testes were small (fig.

Therapy for congenital adrenal cortical hyperplasia has until recently been surgical. H. H. Young advocated and practiced bilateral sub-total adrenal resection and reported some improvement in his patients. This rather formidable procedure was not widely accepted. Recently, L. Wilkins reported beneficial effects from the use of cortisone. The use of this hormone results in a prompt drop in the excretion of the 17-ketosteroids and progressive virilization may thus be restrained. Plastic procedures are necessary, however, to correct the urethral and vaginal deformity.

*Case 3. L. O. (631375),* admitted to The Mount Sinai Hospital July 1951, was a 5-year old white female with the history of a large clitoris at birth, and recent rapidly increasing body size and presence of pubic hair.

The patient was the first born child of normal parents. She had been born at term weighing 7 pounds, 2 ounces. The mother noted that clitoris was enlarged at birth. Development and growth were otherwise normal until the age of 2 when large body size and growth of pubic hair became evident. At the age of 3 the child was taken to another hospital where complete workup was done and diagnosis



FIG. 3. Case L. O. Five-year old white girl showing characteristic pseudohermaphroditic appearance resulting from congenital cortical hyperplasia.

of congenital adrenal cortical hyperplasia was made. 17-Ketosteroid excretion at that time was 7.8 mg./litre.

The child continued to grow and developed great strength and size. There were frequent attacks of pimples on face. The breasts did not enlarge and no vaginal bleeding occurred. Behavior was that of a normal girl.

Physical examination revealed a large child with masculinized body contours and presence of pubic hair. Aene of the face was present. The clitoris was a penis-like organ of large size with retractable prepuce. The organ was bound down ventrally and the spongiosum was absent (fig. 3). A vulvar trough of mucous membrane was evident completing the picture of a typical female pseudohermaphrodite. No testes could be made out and no prostate was evident to rectal touch. No abdominal masses or viscera were palpable. The voice was high-pitched. Intelligence was normal for age and behavior was quite feminine. Routine laboratory examinations were within normal limits. The bone age was 10 years. The excretory urograms showed normal upper tracts. No evident suprarenal masses.

Panendoscopy revealed a normal urethral channel leading upwards to bladder from anterior aspect of vulvar opening. Upon withdrawing the instrument, a communication posteriorly was noted which led into a long tube lined by mucous membrane. Hippuran injected into this tube outlined a normal vagina.

17-Ketosteroid excretion, 21.66 mg. litre, 11 Oxysteroids, 0.49 mg. litre. The patient was given a course of cortisone therapy, 25 mg. by mouth t.i.d. and there was a prompt response with 17-ketosteroids falling to normal limits.

Comment: Case of precocious sexual maturation of hetero-sexual type with pseudohermaphroditism typical of congenital adrenal cortical hyperplasia. Prompt drop in 17-ketosteroid excretion with the use of cortisone.

#### ADRENAL HYPERPLASIA AND TUMOR IN MALES

Hyperfunction of the adrenal cortex, the result of either hyperplasia or tumor, produces an incomplete precocious sexual maturation in both sexes. Adrenal cortical hyperplasia has a high familial incidence; several siblings may be affected. Because of the co-existence of evidences of adrenal insufficiency in this condition not a few die in infancy. Those who survive go on to remarkable somatic and genital overgrowth. The clinical aspect of cortical hyperplasia and tumor in males is alike. The patients grow rapidly and are quite muscular. Penis and prostate enlarge almost to adult size. The testes, however, remain infantile. Testicular biopsies show some tubular development but the Leydig cells are not activated and spermatogenesis does not occur. The picture of large penis and small testes constitutes dissociated virilization and is an important diagnostic consideration. In both tumor and hyperplasia, the excretion of the 17-ketosteroids is markedly increased; the beta fraction is said to be particularly high in cases of tumor. Perirenal air insufflation and laminography will often outline adrenal tumors. The method recently introduced by Ruiz Rivas whereby air introduced into the presacral space readily ascends the lumbar gutters to outline both perirenal areas has made the procedure both easy and safe. Frequently, however, surgical exploration must be carried out to differentiate between adrenal cortical tumor and hyperplasia. The treatment of tumor is, of course, surgical extirpation.

Bilateral subtotal adrenal resection has been advised for diffuse cortical hyperplasia. Before this is done, it would be advisable to give cortisone therapy for it may well reduce androgenic hyperfunction in boys as well as in girls.

Case 4. C. R. (626852), admitted to The Mount Sinai Hospital June 1951, was a 2 $\frac{1}{2}$  year old Negro boy with history of rapid growth in size, and large genitals. The large penis, which had been noted at age of 6 months, gradually increased in size as did bodily stature. Pubic hair appeared at 2 years and the voice deepened. The patient was the second of three children; other two siblings normal. Child had been well except for convulsive episodes which were associated with fever and tonsillitis. The familial history was negative.

Examination showed a strikingly developed boy with well-proportioned herculean habitus. He was alert and did not appear ill. Fine pubic hair present; no axillary hair. Penis was enlarged to almost adult size; the testes were small (fig.

4). The left kidney could easily be palpated. Blood pressure, 155/70. Bone age, 6; x-rays of skull negative. Excretory urography disclosed a mass above the left kidney pushing the latter downward. Irregular flecks of calcium were scattered throughout the mass. Perirenal air insufflation delineated the mass noted on excretory urography in the region of the left adrenal. Routine laboratory examinations were normal. There was no clinical nor hormonal evidence of Cushing's disease or adrenal insufficiency. 17-Ketosteroids, 96.1 mg./24 hours; and 104 mg./24 hours. No change after cortisone.



FIG. 4. Case C. R. Two and half year old Negro boy showing marked penile enlargement, but infantile testes in case of adrenal cortical carcinoma. Case is one of isosexual incomplete precocious maturation (dissociated virilization).



FIG. 5. Case C. R. Adrenal cortical carcinoma weighing 132 gm. removed from 2½ year old Negro boy. Preoperative 17-ketosteroids, 96 to 104 mg./24 hours.

On June 15, 1951, under general anesthesia, the region of left adrenal was explored. A well encapsulated mass replacing the adrenal was totally removed. It weighed 132 gm. and measured 7 by 6 by 4 cm. in size (fig. 5). The postoperative course was complicated by an intercurrent varicella but was otherwise fairly smooth.

Diagnosis: Adrenal cortical carcinoma with foci of calcification.

Radiation therapy was not administered and child is being followed in the out-patient department. 17-Ketosteroid excretion postoperatively was 3.3 mg. and 2.5 mg./24 hours.

Comment: The foregoing is a case of isosexual incomplete precocious puberty

in a boy of  $2\frac{1}{2}$  years caused by adrenal cortical carcinoma. 17-Ketosteroids were markedly elevated. Perirenal air insufflation outlined an adrenal mass. Operative removal successful with drop in 17-ketosteroids to normal.

## SUMMARY

Precocious puberty can be caused by a number of etiologic factors which may be classified as: 1) constitutional, 2) intracranial, 3) adrenal, 4) gonadal. Hormonal imbalance arising from premature activation of the brain centers or the anterior pituitary produces an isosexual complete maturation in both sexes; both the secondary sexual characteristics and the gonads are well developed. Disturbances of the endocrine mechanism on an adrenal or gonadal level produce an incomplete sexual maturation; the secondary sexual characteristics are strikingly developed, but the gonads themselves are infantile. This distinction between complete and incomplete maturation is an important diagnostic consideration.

Testicular biopsy, perirenal air insufflation, pneumo-encephalography and urine hormone assays play an important role in differentiating the various causative factors.

Cases illustrative of four different types of precocious puberty have been presented together with a description of the methods of diagnosis and of treatment.

Addendum: Since this article was written, cortisone, given in small maintenance doses, has been convincingly demonstrated as the treatment of choice in the long term care of patients of both sexes with adrenal cortical hyperplasia. The absence of clinical response to cortisone and failure of the 17-ketosteroid titre to fall to normal levels has been shown to be an important diagnostic test indicative of adrenal cortical tumor as in case 4.

123 E. 83rd St., New York 28, N. Y.

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## THE EFFECT OF ANTIBIOTICS ON HUMAN SPERMATOZOA

HARRY SENECA AND DIANE IDES

*From the College of Physicians and Surgeons, Columbia University, New York, N. Y.*

Bull spermatozoa remained fertile for three to four days when the semen was diluted in 4 parts of 2.9 per cent sodium citrate and 1 part egg yolk.<sup>1, 2, 3</sup> Although adequate bacterial control was not obtained yet the addition of 0.3 per cent sulfanilamide increased the fertility of the spermatozoa.<sup>4, 5, 6</sup>

Penicillin in excess of 1,000 units per ml. of semen showed decreased viability of the spermatozoa during long storage even though there was retardation of bacterial growth and depression of glucose utilization.<sup>7, 8</sup> In such a mixture penicillin was stable at 4.5 degrees C for as long as 16 days. If the concentration of penicillin did not exceed 1,000 units per ml. semen could be stored for longer periods.<sup>9</sup> Penicillin controlled bacteria slightly better than sulfanilamide.<sup>10</sup>

Streptomycin in 0.3 mg. or more per ml. of diluted semen did not manifest any toxic effect on spermatozoa,<sup>11, 12</sup> but 1 mg. per ml. decreased the viability of spermatozoa.<sup>13</sup>

Dihydrostreptomycin in concentrations between 100 to 900 gamma per ml. had no effect on the spermatozoa for 20 days.<sup>14</sup> Synergistic effect was reported on the bacterial growth when 1,000 units per ml. of penicillin and 1,000 gamma per ml. of streptomycin were added to the semen without reducing the viability of the spermatozoa for 20 days.<sup>15, 16</sup>

One hundred gamma per ml. of aureomycin could be added without spermicidal effect. Two mg. per ml. of polymyxin D, B or E had no toxic effect.<sup>17</sup> Aureomycin in 125 to 250 gamma per ml. was toxic.<sup>12</sup> Chloromycetin was toxic in concentrations of 1 to 2 mg. per ml. of diluted semen.<sup>12</sup>

Terramycin in a concentration of 20 gamma per ml. was not toxic.<sup>18</sup> Five

This work has been supported by Charles Pfizer and Company, Brooklyn, N. Y.

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hundred gamma dihydrostreptomycin and 0.6 per cent sulfanilamide added to bull semen diluted in egg yolk and 2.9 per cent buffered sodium citrate is the best preservative.<sup>18</sup>

Studies on the effect of antibiotics on human spermatozoa are very scanty. Carminati reported that chloromycetin inhibited human spermatozoa in 0.5 to 2.0 mg. per ml. in the first few minutes; tyrothrycin in 66.6 gamma per ml. immobilized spermatozoa in 10 minutes.<sup>19</sup>

#### MATERIAL AND METHODS

Human sperms were collected directly into sterile petri dishes or test tubes from young healthy adults. A sperm count was made and the number of spermatozoa per ml. of semen was determined in a blood counting chamber.

The water soluble antibiotics and isonicotinic acid hydrazide (Cotinazin, Pfizer) were dissolved serially in sterile saline. The nonwater soluble antibiotics, namely thiolutin, rimocidin and fumagillin were dissolved in 70 per cent ethyl alcohol and then serially diluted in sterile saline. A mixture of equal amounts of the diluted antibiotic and human semen containing about 50 to 70 million spermatozoa per ml. were observed in a hanging drop preparation under the microscope and the motility as well as the structure of the spermatozoa were recorded under the low and high power objectives. The hanging drop slides were kept at room temperature.

Penicillin, bacitracin, polymyxin, Terramycin, aureomycin, viomycin, neomycin, Magnamycin, Rimocidin, Thiolutin, fumagillin and isonicotinic acid hydrazide were tested in the concentration shown.

##### *Penicillin*

|                  | 0' | 30' | 60' | 104' | 129' | 144' |
|------------------|----|-----|-----|------|------|------|
| 25,000 units/ml. | 4+ | 4+  | 4+  | ++   | ++   | —    |
| 2,500 units/ml.  | 4+ | 4+  | 4+  | 4+   | 4+   | 4+   |

##### *Streptomycin*

|            | 0' | 28' | 60' | 68' | 108' | 133' |
|------------|----|-----|-----|-----|------|------|
| 50 mg./ml. | 4+ | 4+  | 4+  | ++  | —    | —    |
| 5 mg./ml.  | 4+ | 4+  | 4+  | 4+  | 4+   | 3+   |

##### *Bacitracin*

|                | 0' | 30' | 60' | 90' | 110'           | 120' | 160'           | 209' | 240' |
|----------------|----|-----|-----|-----|----------------|------|----------------|------|------|
| 1250 units/ml. | 4+ | 4+  | 4+  | ++  | Moderate lysis |      | complete lysis |      | —    |
| 125 units/ml.  | 4+ | 4+  | 4+  | 4+  | 4+             | ++   | +              | —    | —    |
| 12.5 units/ml. | 4+ | 4+  | 4+  | 4+  | 4+             | 3+   | 3+             | +    | —    |

<sup>19</sup> Carminati, G. M.: Boll. ist Sieroterap. Milan, 30: 550, 1951.



[illegible][illegible]

|                | 0' | 20' | 57' | 65' | 116' | 158' | 186' |
|----------------|----|-----|-----|-----|------|------|------|
| 12.5 mg./ml.   | 3+ | 3+  | 3+  | ++  | —    | —    | —    |
| 1 25 mg /ml.   | 4+ | 4+  | 4+  | 4+  | 3+   | ++   | ++   |
| 0.125 mg./ml.  | 4+ | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |
| 0 0125 mg./ml. | 4+ | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |

[illegible]

|                 | 0' | 9' | 33' | 64' | 133' | 173' | 202' |
|-----------------|----|----|-----|-----|------|------|------|
| 6.25 mg./ml.    | 4+ | 4+ | 4+  | 4+  | 4+   | 4+   | 3+   |
| 0.625 mg./m.    | 4+ | 4+ | 4+  | 4+  | 4+   | 4+   | 4+   |
| 0 0625 mg /ml.  | 4+ | 4+ | 4+  | 4+  | 4+   | 4+   | 4+   |
| 0.00625 mg /ml. | 4+ | 4+ | 4+  | 4+  | 4+   | 4+   | 4+   |

[illegible]

*Rimocidin*

|                      | 0' | 20' | 30' | 60' | 64' | 101' | 149'   | 174' |
|----------------------|----|-----|-----|-----|-----|------|--------|------|
| 1250 gamma/ml.       | +  | —   | —   | —   | —   | —    | —      | —    |
| 125 gamma/ml.        | 4+ | 4+  | 4+  | 4+  | 4+  | 4+   | + or — | —    |
| 12.5 gamma/ml.       | 4+ | 4+  | 4+  | 4+  | 4+  | 4+   | 3+     | 3+   |
| 1.25 gamma/ml.       | 4+ | 4+  | 4+  | 4+  | 4+  | 4+   | 4+     | 4+   |
| 0.125 gamma/ml. ...  | 4+ | 4+  | 4+  | 4+  | 4+  | 4+   | 4+     | 4+   |
| 0.0125 gamma/ml. . . | 4+ | 4+  | 4+  | 4+  | 4+  | 4+   | 4+     | 4+   |

*Thiolutin*

|                    | 0' | 30' | 70' | 90' | 110' | 155' | 180' |
|--------------------|----|-----|-----|-----|------|------|------|
| 1250 gamma/ml. ... | —  | —   | —   | —   | —    | —    | —    |
| 125 gamma/ml.      | 4+ | 4+  | +   | +   | +    | —    | —    |
| 12.5 gamma/ml.     | 4+ | 4+  | 4+  | 4+  | 4+   | +    | +    |
| 1.25 gamma/ml.     | 4+ | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |
| 0.125 gamma/ml.    | 4+ | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |
| 0.0125 gamma/ml.   | 4+ | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |

*Fumagillin*

|                  | 0' | 30' | 60' | 90' | 115' | 160' | 185' |
|------------------|----|-----|-----|-----|------|------|------|
| 1250 gamma/ml.   | —  | —   | —   | —   | —    | —    | —    |
| 125 gamma/ml.    | 4+ | 4+  | 4+  | 3+  | 4+   | +    | —    |
| 12.5 gamma/ml.   | 4+ | 4+  | 4+  | 4+  | 3+   | 3+   | 3+   |
| 1.25 gamma/ml.   | 4+ | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |
| 0.125 gamma/ml.  | 4+ | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |
| 0.0125 gamma/ml. | 4+ | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |

*Isonicotinic acid hydrazide*

|               | 0' | 20' | 44' | 66' | 76' | 95' | 145' | 184' | 215' |
|---------------|----|-----|-----|-----|-----|-----|------|------|------|
| 10 mg/ml.     | 4+ | 4+  | 4+  | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |
| 1 mg/ml.      | 4+ | 4+  | 4+  | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |
| 0.1 mg/ml.    | 4+ | 4+  | 4+  | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |
| 0.01 mg/ml.   | 4+ | 4+  | 4+  | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |
| 0.001 mg/ml.  | 4+ | 4+  | 4+  | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |
| 0.0001 mg/ml. | 4+ | 4+  | 4+  | 4+  | 4+  | 4+  | 4+   | 4+   | 4+   |

+ means motile spermatozoa

— means non-motile or dead spermatozoa.

## RESULTS

Penicillin in 2,500 units per ml. had no effect over a period of 144 minutes but in 25,000 units per ml. showed reduction of motility in 104 minutes and in 144 minutes the spermatozoa were completely immobilized.

Streptomycin in 5 mg. per ml. had no effect in 108 minutes but showed some reduction of motility in 133 minutes. In 50 mg. per ml. the motility of spermatozoa was reduced about 50 per cent in 68 minutes and completely immobilized in 108 minutes.

Bacitracin in  $12\frac{1}{2}$  units per ml. had no effect on spermatozoa in 110 minutes but in 120 minutes there was reduction in motility and complete immobility in 240 minutes. In 125 units per ml. the spermatozoa lost their motility in 209 minutes. In 1,250 units per ml. there was marked reduction of motility in 90 minutes, loss of motility in 110 minutes and complete lysis in 160 minutes.

Polymyxin in concentrations of 10 to 10,000 units per ml. had no effect on the spermatozoa. In concentrations of 10 to 100 units per ml. the motility of the spermatozoa was increased indicating that there was some sort of stimulation.

Terramycin in  $12\frac{1}{2}$  mg. per ml. immobilized the spermatozoa in 7 minutes. In concentrations ranging from 0.0125 mg. to 1.25 mg. it had no effect on the spermatozoa in 240 minutes. Twelve and one half mg. per ml. of aureomycin inactivated spermatozoa in 116 minutes and 1.25 mg. per ml. reduced the motility of spermatozoa by 50 per cent in 158 minutes.

Viomycin in a concentration of 0.0025 mg. per ml. had no effect whatsoever in 215 minutes. In 0.25 mg. per ml. there was reduction of motility in 194 minutes and complete immobility in 215 minutes. In 2.5 mg. per ml. there was some reduction of motility in 44 minutes and complete immobility in 215 minutes. In 25 mg. per ml. moderate reduction of motility in 22 minutes and complete immobility in 144 minutes.

Neomycin in concentrations of 6.25 mg. to 0.00625 mg. per ml. had practically no effect on the motility of the spermatozoa over a period of 202 minutes.

Magnamycin had no effect on spermatozoa in a concentration of 0.001 mg. per ml. over a period of 215 minutes but there was slight reduction of motility in 0.1 mg. per ml. in 95 minutes, and complete immobility in 215 minutes. In 1 mg. per ml. partial reduction of motility in 20 minutes and complete immobility in 95 minutes. In 10 mg. per ml. moderate loss of motility in 20 minutes and complete immobility in 44 minutes.

Rimocidin had no effect in 1.25 gamma per ml in 174 minutes, but in 125 gamma per ml. there was marked loss of motility in 149 minutes and complete immobility in 174 minutes, while in 1250 gamma per ml. there was complete immobility in 20 minutes.

Thiolutin completely immobilized spermatozoa in 1250 gamma per ml. There was marked immobility in 125 gamma per ml. in 70 minutes and complete immobility in 155 minutes. In 12.5 gamma per ml. there was moderate immobility in 110 minutes. In one and a quarter gamma per ml. it had no effect in 180 minutes.

Fumagillin in 1250 gamma per ml. showed immediate complete immobility. In 125 gamma per ml. there was partial immobility in 90 minutes and complete immobility in 185 minutes. In a concentration of 1.25 gamma per ml. there was no effect in 185 minutes.

Isonicotinic acid hydrazide in concentrations ranging from 0.0001 mg. per ml. to 10 mg. per ml. had no effect on the motility of spermatozoa in 215 minutes. As a matter of fact, there was a mild increase in the motility of the spermatozoa.

## DISCUSSION

Generally speaking, penicillin, streptomycin, Terramycin, aureomycin and neomycin have practically no effect on human spermatozoa. Viomycin and Magnamycin show a slight toxic effect, while Rimocidin, Thiolutin, fumagillin and bacitracin are toxic. Polymyxin is completely nontoxic and has some stimulating effect on the motility of human spermatozoa. Isonicotinic acid hydrazide is nontoxic.

The commonly used antibiotics in therapeutic concentrations have no effect on the vitality of human spermatozoa. Probably bacitracin in large doses may have some toxic effects. Rimocidin and Thiolutin are too toxic therefore cannot be used for systemic treatment. Fumagillin is being used in the treatment of amebiasis, and it may exert some toxic effect on the spermatogenic cells.

## SUMMARY AND CONCLUSION

The *in vitro* effect of antibiotics on human spermatozoa indicate that polymyxin has stimulating effect; isonicotinic acid hydrazide is non-toxic; penicillin, streptomycin, Terramycin, aureomycin and neomycin are slightly toxic; Magnamycin and viomycin are mildly toxic; while bacitracin, fumagillin, Rimocidin and Thiolutin are moderately toxic.

## PRESACRAL OXYGEN INJECTION

FRED LERMAN, JAMES G. M. HARPER, ARTHUR D. HERTZBERG  
MICHAEL H. BERMAN AND PHILIP H. LERMAN

*From the Department of Urology, Veterans Administration Hospital, Bronx, N. Y.*

Recently, M. Ruiz Rivas<sup>1</sup> described a technique whereby generalized subserous emphysema could be produced by means of a single injection of oxygen. This is based on an anatomic concept of the continuity of all the subserous cellular tissues of the body.

We became interested in the application of this technique to urological diagnosis. Foremost was the possibility of obtaining bilateral simultaneous perirenal oxygen contrast studies with a single injection.

The procedure proved satisfactory in our hands and gave such substantial diagnostic aid that we are reporting our experiences in the belief that others will find the procedure equally gratifying.

Most impressive have been: 1) simplicity of technique; 2) uniformly good results; 3) minimal discomfort to the patient; 4) few complications; 5) readily available equipment.

### EQUIPMENT

The equipment used is: 1) 18 gauge, three or four inch needle; 2) 2 cc syringe with intradermal needle; 3) 1 per cent novocain; 4) 10 cc syringe; 5) two 1000 cc infusion flasks; 6) two venopak sets; 7) oxygen.

### TECHNIQUE

1) Prepare two 1000 cc infusion flasks, one with water and the other with oxygen as for infusion, with a venopak set connected to each. The oxygen bottle is prepared by attaching a catheter and connecting glass tube to an oxygen tank and running oxygen through the empty bottle for three minutes at a rate of 10 litres/min. An alternate method is to fill the bottle by means of fluid displacement; i.e., to run oxygen into a full bottle with the outlet open until all of the fluid has been displaced. Then close both the inlet and outlet until ready to use.

2) Eliminate the preceding meal and give seconal 0.1 gm. 1 hour prior to the procedure.

3) Place the patient in knee-chest position, with pillows or bolster under the abdomen for comfort. (The more exaggerated the knee-chest position, the easier will be the introduction of the needle.)

4) Prepare the skin of the sacrococcygeal area and drape with sterile towels.

5) Introduce the left index finger into the rectum, and palpate the tip of the coccyx and the hollow of the sacrum.

6) Raise a skin wheal with 1 per cent novocain, midway between the anus and the tip of the coccyx, and 2 cm. to the right of midline.

<sup>1</sup> Ruiz Rivas, M.: Roentgenological diagnosis: Generalized subserous emphysema through single puncture. *Am. J. Roent. & Radium Therapy*, 64: 723-734, 1950.

7) Introduce the 18 gauge three or four inch needle through the skin wheal, and direct the point into the hollow of the sacrum, controlling direction by the palpating finger in the rectum (fig. 1). The needle passes to the right of the coccyx so that the point lies between rectum and sacrum, about 2 cm. above the sacro-coccygeal joint.

8) Aspirate with a 10 cc syringe to assure that the needle point is not in a blood vessel.

9) Inject 10 cc of air through the same syringe to make sure that the needle point is not caught in a fold of rectal wall or against periosteum, either of which impedes the flow of oxygen. (If found caught, minimal readjustment is readily made.)

10) Introduce the oxygen through the needle from the previously prepared bottle. The rate is about 100 cc/min., and the total amount can vary from 600 cc to 1500 cc. (We have found 1000 cc optimal in most cases.)

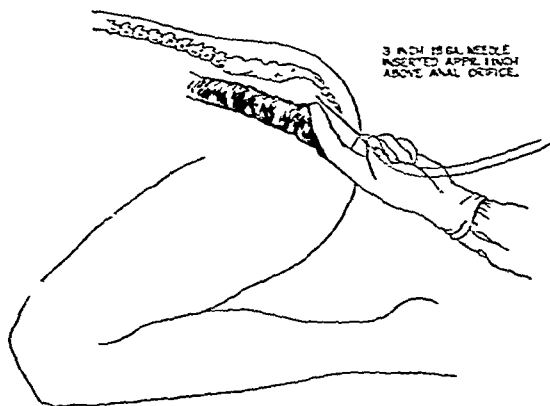


FIG. 1. Sagittal section showing position of needle

The infusion flask containing water is suspended on a regular infusion stand. The outlet tubing is connected to the inlet of the oxygen flask. The oxygen flask is placed upright about three feet below the level of the water flask. The outlet tubing from the oxygen flask is connected to the needle in the patient. Rate of flow can be increased by increasing the distance between the two bottles.

The apparatus we have devised is especially satisfactory because it gives an immediate measurement of the total amount of oxygen introduced, and its rate of introduction.

11) With the usual factors take roentgenograms immediately, and in 1 hour, 4 hours and 24 hours—with variations in position and timing as the situation demands. Between exposures the patient follows his normal hospital routine.

The oxygen distribution can be readily controlled. If it has largely settled on one side and emphasis is desired on the opposite side, merely placing the patient in the lateral position, with the desired side uppermost will cause movement of the oxygen to that side in 15–30 minutes. If signs, such as crepitation in the neck, show that the mass of oxygen has risen above the diaphragm, placing the patient

in the Trendelenburg position will cause enough oxygen to return to the sub-diaphragmatic space to insure clear delineation.

#### CLINICAL APPLICATIONS AND CASE REPORTS

1) The normal roentgenogram obtained following presacral oxygen injection.

*Case 1.* (BVAH No. 143 100.) R. H., a 23 year old white man, was admitted with a 5-day history of bilateral loin pain radiating anteriorly across the abdomen to each testicle. Diagnostic studies revealed the lesion to be a small radiolucent calculus in the lower third of the right ureter, which subsequently passed without operation. Presacral oxygen injection combined with retrograde pyelogram demonstrated (fig. 2) normal adrenal spaces, renal outlines, and psoas margins.



FIG. 2. Case 1. Normal roentgenogram following presacral oxygen injection, demonstrating medial arcuate ligament of diaphragm on both sides, right adrenal shadow of normal size, left adrenal space without distortion, both kidney outlines without irregularities, and sharp straight psoas margins.

The value of the normal roentgenogram following presacral oxygen injection lies in ruling out lesions of the aforementioned visualized structures.

At present we are utilizing both this procedure and the classical method of perirenal air insufflation in a series of patients in order to make a more exact comparison. The results of this series will be reported later.

2) Failure of oxygen to clearly outline the retroperitoneal structures suggests that these potential spaces are occupied by tumor or are closed by inflammatory reaction.

*Case 2.* (BVAH No. 143 267.) J. V., a 29 year old white man, was admitted with a 5-year history of recurrent dull aching in the right lumbar region. Excretion urography revealed a normal left collecting system and calculous disease on the right without evidence of renal function. Presacral oxygen injection

showed normal oxygen penetration of the left retroperitoneal space (fig. 3), and a failure of oxygen to penetrate the right retroperitoneal space. Right nephrectomy was performed. The operative findings were a right calculous pyonephrosis with marked perinephritis and peri-ureteritis.

3) Examination can be more searching by combining this technique with excretion urography, retrograde pyelography, or aortography.

*Case 3.* (BVAH No. 141 161.) E. W., a 39 year old white man, was admitted with gouty arthritis and seen by the urology service in consultation for hypertension averaging 180/120. Excretion urography showed diminished excretion by the right kidney. Phenolsulfonphthalein clearance was 30 per cent in 10 minutes from the left side. A ureteral catheter met an impassable obstruction at 4 cm. on the right side. The possibility of silent obstruction by nonopaque uric

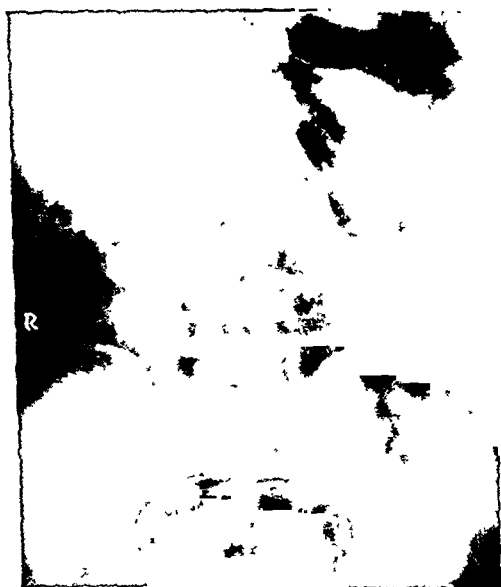


FIG. 3. Case 2. Note good delineation of psoas margin, renal and adrenal structures on left, and failure of oxygen penetration on right due to inflammatory reaction.

acid calculi could not be ruled out. Presacral oxygen injection combined with Woodruff ureteropyelography revealed the right kidney to be small with very little cortex (fig. 4, B). A Woodruff ureteropyelogram without presacral oxygen did not reveal this cortical damage (fig. 4, A). A nephrectomy was advised but was refused by the patient.

4) Irregularities in the shape of a kidney stand out because the outline of the organ is sharply delineated.

*Case 4.* (BVAH No. 137 495.) I. Z., a 42 year old white man, was admitted with pain in the left arm. Biopsy of a destructive lesion of the left humerus showed adenocarcinoma, suggestive of renal origin. Excretion urography was nondiagnostic. Retrograde pyelography showed no obvious distortion of the calyceal pattern of either kidney. Presacral oxygen injection with a left lateral



retrograde pyelogram demonstrated a large tumor of the upper pole of the left kidney (fig. 5, *B*). Left lateral retrograde pyelography without presacral oxygen



FIG. 4. Case 3 *A*, shows right ureteropyelogram without definite kidney outline. *B*, similar ureteropyelogram taken after presacral oxygen injection demonstrates negligible amount of remaining cortex on right.



FIG. 5. Case 4. *A*, left lateral pyelogram showing no apparent deformity of calyceal system or of renal outline. *B*, similar pyelogram taken after presacral oxygen injection reveals tumor of upper pole of left kidney

showed no obvious deformity (fig. 5, *A*). A left nephrectomy was performed and the preoperative diagnosis was confirmed. Two weeks later a left scapulo-humeral amputation was performed. The final pathological diagnosis was adenocarcinoma

of the left kidney with metastases to the left humerus. At present the patient is alive and well, and is free from demonstrable metastases nine months post-operatively.

#### RESULTS AND COMPLICATIONS

To date we have performed 50 oxygen injections. There has been no difficulty with the technique.

We have observed the following complications:

1) The needle point was introduced into the rectum in 2 patients. This caused no immediate or late injury. Satisfactory oxygen injection was obtained in each case after readjustment of the needle.

2) Three patients complained of abdominal pain. One was relieved within 5 minutes by the Trendelenburg position. The second vomited with complete relief. The third patient had severe pain simulating renal colic and required the Trendelenburg position and sedation. Since we have decreased the rate of oxygen flow to 100 cc/min., and have used 1000 cc of the gas rather than 1500 cc this complication has not recurred.

3) In 1 patient crepitus developed in the superficial tissues of the neck, without pain. This was relieved by the Trendelenburg position.

4) In 2 patients shoulder pain developed, relieved by placing them in the supine position.

Oxygen embolism has not occurred in this series. Realizing that it is a possibility, however, whenever large amounts of oxygen are introduced into any body cavity, we feel it worthwhile to mention the treatment. Recently emphasized by Hollander,<sup>2</sup> satisfactory therapy consists of placing the patient in the left lateral recumbent position until sufficient absorption has taken place to completely relieve the obstruction. This may take several hours.

#### SUMMARY

A new technique for visualization of the retroperitoneal space, originally proposed by M. Ruiz Rivas, is described and discussed.

This technique of presacral oxygen injection is simple, and is apparently innocuous.

It has wide applicability in urology.

It has been a useful addition to our diagnostic armamentarium.

Addendum: At the time of publication we have performed more than 200 presacral oxygen injections. No additional complications have occurred. Since the results with this additional experience have been equally as gratifying as those described above, we feel even more strongly that this procedure should be an integral part of our diagnostic armamentarium.

We wish to express our thanks and appreciation to our chief consultant, Dr. Archie L. Dean, and to our attending staff, without whose encouragement, aid and suggestions we would not have been able to complete this project successfully.

<sup>2</sup> Hollander, A. G.: Air embolism in pneumoperitoneum. J. A. M. A., 147: 569-570, 1951.

## PERIRENAL INSUFFLATION WITH ARTERIOGRAPHY

FRANK C. HAMM AND HARRISON C. HARLIN

Urography, both retrograde and excretory, as well as the microscopic study of wet and stained urine specimens, kidney function tests, urine cultures and similar procedures will yield accurate diagnoses in most instances. Yet, occasionally, a case presents an unusual problem in which these procedures either cannot be advantageously utilized or, if used, fail to give sufficient information. The use of perirenal insufflation of a gaseous medium and translumbar arteriography have enabled us to make diagnoses that could not have been made by other methods. While these two procedures, in the past, have not enjoyed widespread popularity, recent modifications in the technique will, in our opinion, elevate them to usefulness in selected cases. We propose to discuss our experiences in over 200 cases wherein bilateral perirenal insufflation of air or oxygen by the paracoccygeal approach and translumbar arteriography were used singly or in combination, citing and illustrating specific instances in which their utilization proved invaluable.

### PERIRENAL INSUFFLATION

In 1921, Carelli<sup>1</sup> proposed the introduction of a gaseous medium directly into the perirenal space. The contrasting shadow thrown by the gas on the roentgenogram aided materially in the delineation of the renal outline, and made possible sharper visualization of renal cysts and tumors. The abnormal and occasionally the normal adrenal gland similarly could be outlined, since the gas infiltrates into the retroperitoneal space. It was not until 1935 that Cahill,<sup>2</sup> through his monumental work on the adrenals, brought about a revival of the procedure. He has adequately described the technique in which approximately 500 cc air, oxygen, carbon dioxide or helium are introduced into the perirenal space through a needle inserted in the flank on the side to be investigated. While a portion of the gas may pass over to the opposite side, the amount is inconstant so that a separate injection, on the other side, is usually required when bilateral visualization is desired. There is always the chance that a needle introduced into this area may puncture the kidney with subsequent hemorrhage, may irritate the diaphragm, or, what is more serious if air is injected, may enter a blood vessel with resulting embolism.

The aforementioned technique was used to a limited extent in our clinic, but the injection of a gas directly into an area containing large vessels was regarded as hazardous. For the past 18 months, at the Brooklyn Veterans Administration Hospital and at The Brooklyn Hospital, we have used a procedure whereby air or oxygen is introduced into the retroperitoneal space through a needle which is inserted between the coccyx and rectum, a technique similar to that suggested by Ruiz Rivas.<sup>3</sup> The gas rapidly diffuses on both sides so that a simultaneous bi-

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 20, 1952.

<sup>1</sup> Carelli, H. H.: *Bull. et mem. Soc. med. d. hop. de Par.*, 45: 1409, 1921.

<sup>2</sup> Cahill, G. F.: *J. Urol.*, 34: 238, 1935.

<sup>3</sup> Ruiz Rivas, M.: *Rev. clin. espan.*, 25: 206, 1947.

lateral perirenal aerogram is obtained from a single injection. The steps preceding administration of the gas are as follows:

- 1) The patient is placed in a prone position on the roentgen table.
- 2) The region of the coccyx and adjacent buttocks is aseptically prepared and draped.
- 3) If the insufflation is being done as a single procedure, in contrast to its concomitant use with translumbar arteriography or retrograde pyelography, an

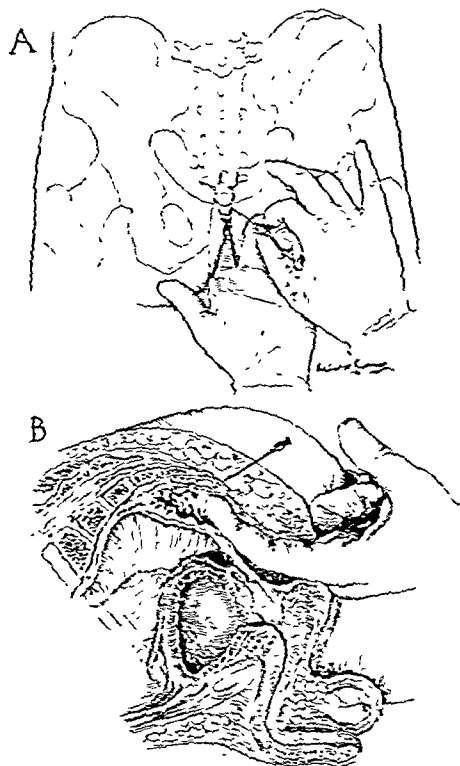


FIG. 1. A, relationship between finger in rectum, coccyx and needle is demonstrated. B, tip of needle is shown in retrorectal space. Depicted as sagittal section.

area approximately 2 cm. from the lateral border of the midcoccyx is infiltrated with local anesthesia.

4) An 18 gauge needle is then inserted and directed toward the lateral portion of the midcoccyx, the index finger of the left hand having been previously introduced into the rectum for palpation and guidance of the needle (fig. 1. A).

5) As the needle comes into contact with the lateral coccygeal border, its point is depressed and introduced into the space between the rectum and coccyx. Inadvertent perforation of the rectum is harmless. The position of the needle is well demonstrated in figure 1. B.

With the needle in position, a 50 cc syringe with a secured two-way stopcock is attached to it and approximately 1000 cc oxygen is introduced into the retro-

peritoneum. Originally, we used filtered air as the insufflating medium, but because of the length of time required for its absorption, we changed to oxygen which is not only absorbed much more rapidly but, in our experience, seems to be more diffusible. Before the injection is started, the needle is aspirated for assurance that no blood vessel has been entered. The principal advantage accruing from this approach is that no vessels of any consequence traverse the area. In fact, no significant structures are encountered; the peritoneal reflection comes off at a higher level.

A roentgen exposure is made after the gas has been introduced. The operator can be assured that the needle is in proper position by feeling the crepitus as the gas passes into the retroperitoneal space. If there is resistance to the injection, the oxygen is probably infiltrating the buttocks. If neither resistance nor crepitation is felt, the gas is undoubtedly entering the colon. These latter circum-



FIG. 2. *A*, bilateral simultaneous perirenal oxygen insufflation demonstrating left adrenal tumor in young woman with adrenogenital syndrome. Adrenal cortical adenoma was found at surgery. *B*, bilateral simultaneous perirenal oxygen insufflation disclosing a massive retroperitoneal tumor on the left which, on exploration, proved to be a sarcoma.

stances should cause no concern as the gas is eventually absorbed without having harmed the patient.

As a rule, the gas diffuses on both sides of the retroperitoneum simultaneously and, by the contrasting shadow it casts on the roentgenogram, outlines any contained masses, the normal ones being the kidney and adrenal on each side. Very occasionally, if the tip of the needle is too far from the midline, diffusion occurs on one side only. Usually, however, the unilateral appearance of the gas signifies some pathologic process on the noninsufflated side. Perinephritic inflammation, scarring from previous operative intervention, or any process which results in a "sealing off" of the retroperitoneal tissues will block diffusion of the medium. Other complications of the procedure consist of a feeling of pressure in the chest if the gas enters the mediastinum; a feeling of fullness and crepitation if it extends to the neck; and an enlargement of the scrotum when it occasionally passes down in this direction. These conditions are more annoying than serious and are relieved as the gas is absorbed.

Perirenal insufflation is possibly of greatest value as a solitary procedure in the investigation of the adrenal glands (fig. 2). Although irregularities of renal outline

are more sharply defined, much more information is derived from the concomitant use of translumbar arteriography, retrograde urography, or, in selected cases, a combination of the three. This is also true in the case of retroperitoneal masses.

#### TRANSLUMBAR ARTERIOGRAPHY

Translumbar arteriography represents a different approach to the study of renal disease by permitting the roentgenographic study of the external and internal renal vascular patterns in normal and abnormal states. While it is not a new procedure, having been introduced by dos Santos in the 1920s,<sup>4</sup> it has recently been revived by Smith and his associates<sup>5</sup> largely because of the development of newer and safer contrast media which eliminate the undesirable sequelae experienced during the early states of the procedure. The technique, which seems



FIG. 3. Translumbar arteriogram with bilateral perirenal insufflation of oxygen. a) Aerogram; b) arterial phase; c) nephrogram effect.

formidable at first, is in reality rather simple, and consists of introducing a contrast medium into the aorta through a needle which is inserted into the great vessel by a translumbar approach. Roentgen exposures are made during the injection and within 15 seconds after the injection has been completed. The technique has been discussed adequately by Smith, therefore we shall not repeat it here.

Intravenous anesthesia has been useful, pentothal sodium being the drug in current usage. Local anesthesia has been found to be inadequate. Preceding the administration of the anesthesia, 0.5 cc of neo-iopax, 75 per cent solution, are introduced into the vein in order to test the patient for any drug sensitivity. If manifestations of allergy develop, the anesthetist has materials on hand to deal with the situation. After induction, the previously described procedure of bilateral simultaneous perirenal insufflation is carried out. As soon as the injection

<sup>4</sup> dos Santos, R. Arch. ital. di chir., 51: 764, 1938.

<sup>5</sup> Smith, P. G., et al.: J. Urol., 66: 145, 1951.

is completed and the exposures made, the films are processed. If they do not prove satisfactory, the injection is repeated once if no contra-indication exists. We do not repeat the injection more than once at a single examination, preferring to use it at a later date if necessary.

At present, interpretations of arteriograms may be likened to those of urograms in the early days of retrograde pyelograms. The roentgenographic findings can be interpreted only by repeated, careful and precise examination, correlating them with urographic data and findings at surgery. Although all of the infra-diaphragmatic branches of the aorta are probably not visualized at any one study, all will be seen at various times. While the urologist's main interest lies in the main and accessory as well as in the aberrant renal vessels, other arteries such as the splenic, hepatic, superior mesenteric, etc. may cause confusion by overlying the renal vessels and renal parenchyma. Each vessel is carefully traced

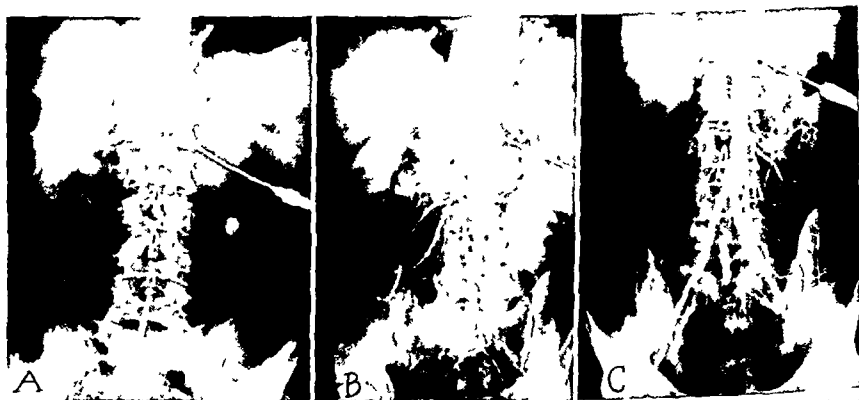


FIG. 4. A, direct injection (without ill effect) into celiac artery resulting in visualization of its three main branches—the hepatic, left gastric and splenic arteries. B, superior mesenteric artery. C, inferior mesenteric artery.

from its point of origin as far as possible toward its termination. The use of bilateral simultaneous gas insufflation, which outlines the renal borders as well as any associated mass, aids in limiting the distal extension of the small terminal renal vessels. Figure 3 demonstrates a normal arteriogram; other vessels that may be outlined are shown in figure 4.

The renal arteries branch from the aorta at the approximate level of the second lumbar vertebra, the left originating, as a rule, at a slightly higher level than the right. The first division of each renal vessel (artery) occurs close to or within the hilum of the kidney, and within the renal sinus the branches become arranged in a dorsal and ventral group behind and in front of the subdivisions of the ureter. As the arteries enter the substance of the kidney, they divide and the larger arteries lie in the intervals between the pyramids. These are known as the *interlobar arteries*. These vessels divide, in turn, and cross over the base of the pyramids to form incomplete arches, the *arcuate arteries*. These "arches" give off a number of vessels, known as the *interlobular arteries*, which pass toward the

surface of the kidney at regular intervals. The vascular arrangement is demonstrated in figure 5. The presence of more than one renal artery is not uncommon, and accessory vessels are seen to enter either pole on numerous occasions.



FIG. 5. *a*, Submaximal injection into main left renal artery showing extra- and intrarenal vascular pattern in portion of kidney supplied by this vessel. Note that a small portion of upper pole of kidney is supplied by a polar artery and that no anastomosis is evident between terminal branches of main renal artery and this vessel. This is further demonstrated by the nephrogram effect, *b*.



FIG. 6. Arteriogram disclosing arteriovenous fistula of renal vessels in young white man suffering from increasing hypertension following shell fragment wound of the right flank. (Arrow points to vein which overlies involved artery.) Exploratory operation confirmed presence of this fistula between main right renal artery and vein. Nephrectomy resulted in fall of blood pressure to normotensive levels 1 year following procedure.

Arteriography is of value in demonstrating obstructing aberrant vessels at the ureteropelvic junction, arterial aneurysms of the renal artery, fistulas between the renal artery and vein (fig. 6), vascular obstruction by embolism and thrombosis. Visualization of the vascular supply in cases of congenital anomalies such



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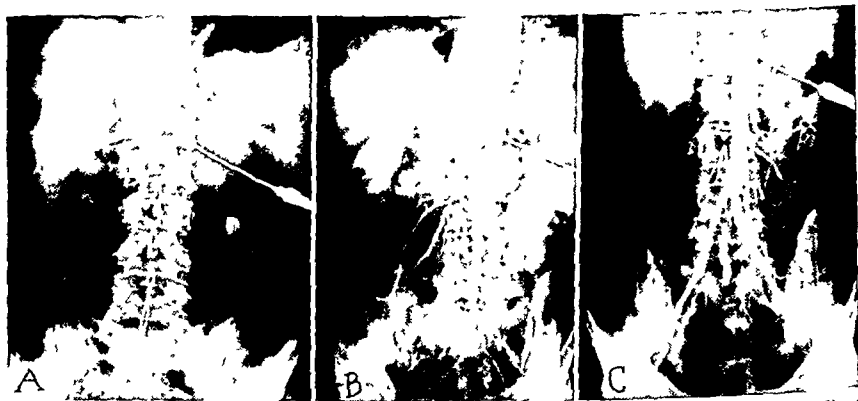


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as horseshoe kidney (fig. 7, *A* and *B*) and fused ectopia (fig. 7, *C* and *D*), affords information as to the number and position of the vessels and the feasibility of

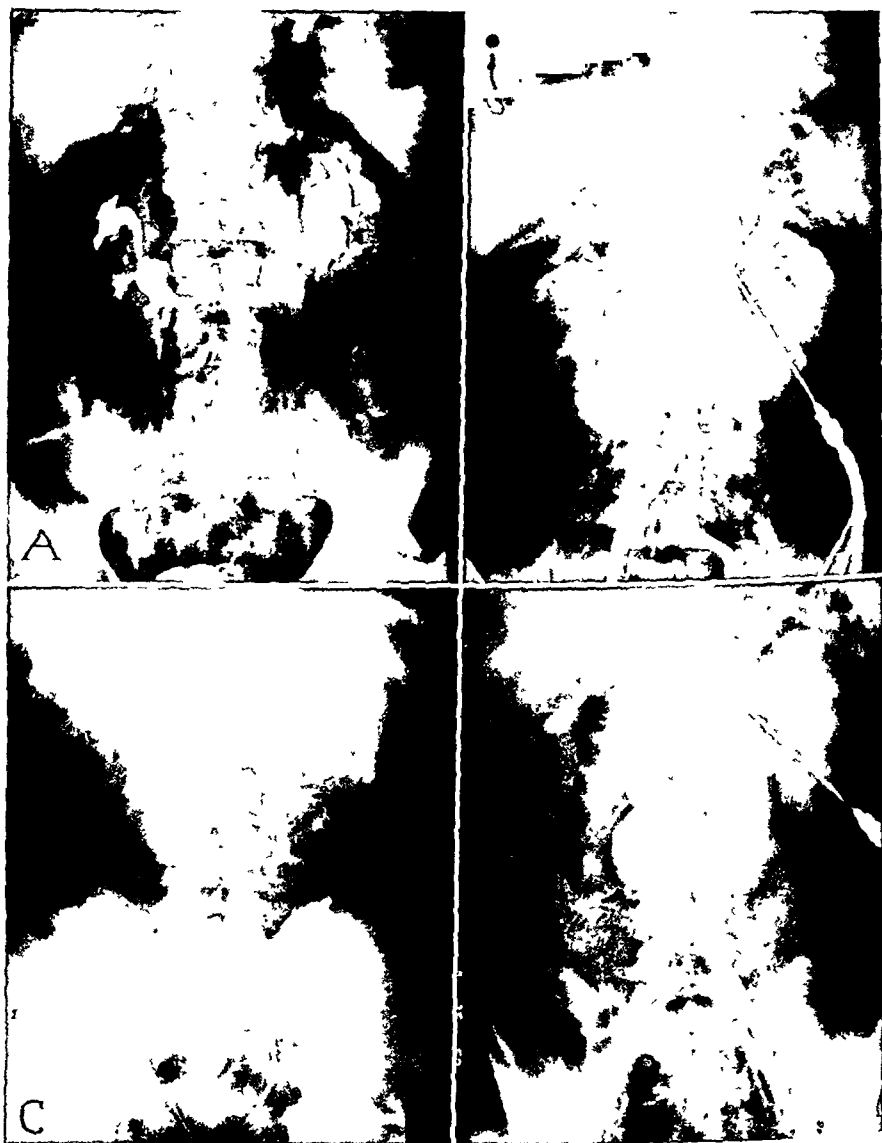


FIG. 7. *A*, retrograde urogram combined with bilateral aerogram in a horseshoe kidney; *B*, arteriogram revealing a relatively vascular isthmus. *C*, retrograde urogram of crossed ectopia with fusion. *D*, arteriogram indicating adequate blood supply to each kidney with a relatively avascular isthmus.

surgical resection. In considering the possibility of heminephrectomy for disease in a portion of a double kidney, the distribution of the blood vessels, as outlined by the contrast medium, is a determining factor. In a given case of

hypertension, with associated renal disease—hypoplasia, hydronephrosis—the evidence of a markedly impaired blood supply to that kidney may suggest the advisability of nephrectomy. Arteriography completes the examination in cases of hydronephrosis when operative intervention is indicated and plastic repair contemplated. Since a kidney is no better than its blood supply, the finding of a paucity of the smaller renal vessels associated with marked deformity of those of larger caliber might influence the operator in favor of nephrectomy. Arteriograms may aid materially in the diagnosis of extrarenal and retroperitoneal tumors, both primary and secondary, since these masses may not only displace the kidney, but also cause distortion of the main renal vessel and, occasionally, a metastatic node may be outlined by the surrounding blood vessels. We demonstrated the latter in a previous publication.<sup>6</sup>



FIG. 8. Arteriogram showing right ectopic kidney with blood supply from aorta just above bifurcation, and from external iliac. Note opacification of parenchyma of this kidney which could not be demonstrated by excretory or retrograde urography.

On occasions, excretory urograms fail to visualize a kidney, and for one reason or another retrograde visualization is impossible. The demonstration of the vascular pattern of the involved kidney may go far in the determination of the probable nature of the disturbance (fig. 8). In polycystic kidney disease, translumbar arteriography serves a twofold purpose: 1) The demonstration of increasing deformity of the intrarenal blood vessels, thereby heralding a decreasing effectiveness of the blood supply and diminishing renal function. 2) While one kidney may present normal pyelograms with adequate renal function and the other may show deformity suggesting neoplasms or cysts, arteriography serves to differentiate cysts from tumors and, also, may well demonstrate deformities of the apparently normal kidney. Vascular changes are probably the earliest clinical changes that may be recorded in polycystic disease.

Arteriography probably serves its most useful purpose in the differentiation of solitary renal cysts and tumors. In cases of tumor, the arterial phase shows dis-

<sup>6</sup> Hamm, F. C. and Harlin, H. C.: *Brooklyn Hosp. J.*, 10: 3, 1952.

placement of the intrarenal vessels adjacent to the tumor. These vessels are seen to surround and enter the tumor mass. The increased numbers of capillaries and sinusoids are outlined by the contained contrast medium giving a characteristic "puddling" and "laking" effect (fig. 9, *A*). This effect is frequently re-



FIG. 9. *A*, arteriogram showing vascular phase of a typical renal-cell carcinoma. Note large vessels surrounding and entering mass which is site of "pooling," "puddling" and "laking" of injected contrast medium. *B*, nephrogram phase of large renal tumor showing "puddling" effect in region of upper pole. At operation, far advanced infiltrating tumor of upper pole of left kidney was discovered.

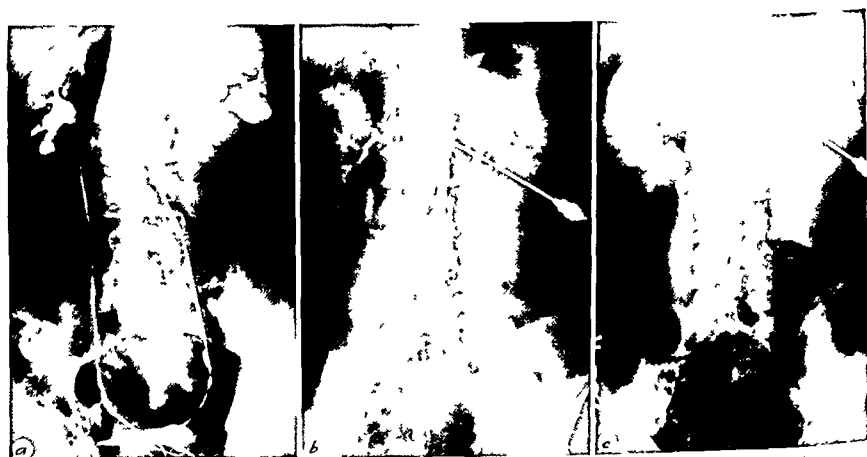


FIG. 10 Solitary renal cyst *a*, Retrograde urogram *b*, Arterial phase revealing vessels displaced by cyst which is clear and avascular. *c*, Nephrogram effect showing opacification of renal parenchyma except in area occupied by cyst.

tained during the nephrogram phase particularly if many sinusoids are present and degeneration is fairly advanced (fig. 9, *B*). The simple serous cyst of the kidney, on the other hand, is avascular, and it overlies or displaces renal parenchyma. Arteriographic studies disclose any or all of the following: a) irregularity of renal outline, b) displacement of the intrarenal vessels adjacent to the parenchymal portion of the mass, c) a relatively clear area, corresponding to the

cystic area, adjacent to the opacified parenchyma on the nephrogram, d) no collection of contrast medium within the area of the mass (fig. 10).

Despite the striking differences of renal cysts and the majority of renal parenchymal tumors, we still subject to surgery those in whom we have made the diagnosis of cyst. This is done because occasionally a parenchymal tumor is found in the wall of a cyst and, unless it has reached a fairly large size and is vascular, it will not be visualized on the arteriogram. While the majority of parenchymal tumors are vascular, there are certain ones such as fibrosarcomas which will not give the typical arteriographic pattern, but may strongly suggest the presence of cyst. It is much better to expose and resect a renal cyst even it happens to be asymptomatic than to miss a tumor contained within the wall, or one that is avascular. There are occasions, however, when the patient's general condition warrants an indefinite delay in surgical exploration although the arteriographic evidence points strongly to cyst.

#### COMPLICATIONS

In our current series of more than 200 cases, we have injected directly into the celiac artery on 2 occasions, into the superior mesenteric artery 5 times, and into the left renal artery in three instances; no noticeable ill effects followed. We have visualized extravasation of the contrast medium both intra- and extramurally without incident. One instance of mild, spontaneously clearing pneumothorax was encountered, and the spinal canal was entered once during the introduction of the needle. No case of acute iodism was encountered.

The only contra-indications to this procedure are severe debilitation, uremia, cardiac failure, severe allergy such as asthma, and sensitivity to the contrast medium.

Recently, in selected cases, we have performed bilateral simultaneous perirenal insufflation, translumbar arteriography and retrograde urography as one examination. This may be done either under spinal anesthesia or intravenous anesthesia, the latter being reserved for the more apprehensive patients. The combination of procedures is ideally suited for those cases which show significant renal abnormalities on excretory urography, and the average total time required to perform them is under 30 minutes.

*80 Hanson Place, Brooklyn 17, N. Y*

## A RÉSUMÉ OF THE EXPERIENCE IN THE MAKING OF 1,500 RENAL ANGIOGRAMS

PARKE G. SMITH

*From the Division of Urology, the Mercy Hospital, Miami, Fla.*

In June 1950, we were privileged to present to the American Urological Association a simplified technique designed to produce a renal angiogram by means of translumbar aortic puncture and to evaluate that procedure on the basis of our experience with over 300 translumbar aortic punctures. A short time later, we proposed a diagrammatic atlas to be used in the interpretation of renal angiograms and later still, discussed the roentgenological interpretation of these films produced by translumbar arteriography. As 2 years have elapsed since we originally presented this technique and as our experience with the procedure now covers a series of approximately 1,500 aortic punctures, we believe we should re-evaluate this technique and review our previous communications with a view of correcting any mistatements, clarifying others, and emphasizing those points that have previously not been sufficiently stressed.

I shall attempt to confine my remarks to this phase of the subject and, in so doing, although I may be presumptuous, I will assume that all of you are familiar with the technique that we have presented as well as the general subject of renal angiography.

Our present series of cases has been completed without mortality and without morbidity of more than minimal degree. We have heard of some two or three accidents following the employment of this technique but we believe that a careful analysis of these unfortunate occurrences would result in the blame being placed elsewhere than upon the procedure itself. As yet, we are not particularly happy with our experience in the use of this procedure in children, as it is extremely difficult to accomplish a satisfactory aortic puncture in the young.

I should first like to clarify the nomenclature to be used in discussing this subject and would suggest that we reserve the term of translumbar arteriography to refer only to the technique of the procedure itself for it is obvious that its field of application can be increased in scope and its usefulness spread over a larger field of investigation by some very simple, minor variations in the technique employed. As a result, we could produce not only the renal angiogram that we as urologists are particularly interested in but a splenic angiogram, a hepatic angiogram; it is also not inconceivable to think that a technique could be developed that would allow the visualization of the distribution of the superior mesenteric artery.

We have made absolutely no change in the apparatus described in our original contribution upon this subject. We still use a polyethylene connecting tube rather than one made of polyvineline, for although the latter has the advantage of being sterilized by heat, it has the great disadvantage of becoming rather inflexible and quite opaque following sterilization, and flexibility of the tube and visibility

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 20, 1952.

of its contents are essential. We cannot emphasize too greatly that the apparatus, although extremely simple, must be of excellent quality and well cared for. The syringe must be glass barrelled with a metal plunger and adequate finger and thumb rings, for it is only with this type of syringe that one can be assured that you will always be able to make the extremely rapid, smooth injection of the contrast medium necessary to produce satisfactory renal angiograms. We use a 6 inch, 18 gauge lumbar puncture type of needle on most patients. Occasionally, in extremely large individuals we will use a 7 or 8 inch needle.

We rarely use more than 12 cc of contrast medium and then only for particular purposes. Any of those ordinarily used for excretory urography are satisfactory in their higher concentrations. Most of our series was made with 70 per cent neo-iopax but recently we have been extremely gratified and pleased with our experience with 70 per cent urokon.

I shall not refer to the roentgenological technique other than to insist that the time of exposure be not more than  $\frac{1}{10}$  of a second and, of course, that the exposure be made by a rotary anode tube with dual control. If the length of exposure is  $\frac{2}{10}$  or  $\frac{3}{10}$  of a second, even though the patient is under anesthesia, there may be a slight movement of one or the other of the kidneys, especially the right. This movement may be sufficient in amount to produce a poor film. The time at which the exposure is made is very precise; a variation of as little as  $\frac{1}{2}$  a second may result in an angiogram of substandard quality. This, of course, requires the utmost co-operation between the urologist and the x-ray technician. The injection must be made as rapidly as possible and the exposure called for just as the last 1 or 2 cc of the contrast medium is being injected.

As soon as the first exposure is made, the needle is immediately withdrawn, the cassette changed, and a second exposure made producing a nephrogram which I believe with further study will eventually become a film of great importance in our study of upper urinary tract disease.

We have performed translumbar aortic puncture under local anesthesia but believe that the intravenous use of sodium pentothal contributes very greatly to the safety of the procedure and favors its being carried out with that degree of precision necessary to regularly produce renal angiograms of high quality.

A correct interpretation of the significance of the variations that are seen in renal angiograms must be based on an accurate knowledge of the arterial pattern of the normal kidney. This can be briefly described as follows: There is a single renal artery whose primary division into two branches occurs near the hilum of the kidney. These two branches again divide into two and division continues in a similar manner until the renal cortex is reached, where the divisions are multiple or "fan-like." These terminal branches of the renal artery pass through the cortex in slightly curved, graceful patterns.

We have always been aware of the frequency with which anomalous renal vessels occur but I am certain that by renal angiography we have learned that the anomalous branching of the renal artery or presence of anomalous renal arteries occurs much more often than we had previously suspected. It is surprising, particularly in the bifid type of kidney, the frequency with which the upper artery is the one of major importance, supplying not only the parenchyma



of the upper pole but usually a fair portion of the anterior surface of the lower pole. We should not contemplate a heminephrectomy without the benefit of the previous knowledge as to the number of renal branches and the extent of their individual distribution. We have been impressed with the great value and importance resulting from the careful establishing of the arterial pattern in all cases of congenital renal anomalies in which renal surgery is contemplated.

One is constantly faced with the necessity of determining the true status of the renal parenchyma, especially the reserve or salvage factor. Although we routinely employ renal functional tests of various types, the information that they give us is of value only in determining the amount of work the renal parenchyma is capable of doing at the time the test is made and that information may be very misleading when it is interpreted as indicating the amount of renal reserve or the salvage factor. This latter is information that can be accurately determined only by renal angiography for the frequently quoted statement that the renal parenchyma is as good but no better than its arteries has become axiomatic.

In a very limited group of cases, this procedure has been of invaluable assistance in establishing the presence of renal infarcts in cases of massive renal hemorrhage, the etiology of which otherwise could not be determined.

In originally discussing the value of renal angiography, we stressed its importance in the differential diagnosis of clear-celled renal tumors and cystic diseases of the renal parenchyma. We emphasized very definitely the pooling or puddling of the contrast medium that is found in the arterial pattern of these clear-cell renal tumors. While we do not wish to retract any of our statements in that respect, we must, in view of our more extensive experience, express these facts in a different manner. We believe that it would be best to emphasize the lack of these areas of pooling or puddling in the cystic diseases where avascularity is almost a universal characteristic and to point out that in the clear-cell renal tumors these areas in which the contrast medium can best be described as pooled or puddled are always present. In certain tumors that have grown extremely rapid or those that are very old, the central portion of the tumor may have lost its vascularity and thus these characteristic, irregular, small areas of accumulation of the contrast medium which we have just referred to may be found only in the periphery of the tumor itself. We are firmly convinced that as our experience increases and as we learn more about the interpretation of renal angiograms that we will approach near perfection in the differential diagnosis of these two conditions.

Our original interest in this subject was prompted by a desire to record preoperatively what we believed to be the cause of renal pain in certain non-urinary obstructed kidneys. We believed that in many of these cases the pain was due to obstruction of the venous outlet of the kidney rather than the urinary.

In order to determine the possibility of such an obstruction, we desired to establish the arterial pattern for study as the venous pattern parallels it very closely. We have continued our investigations in this field and believe that they have been worthwhile. Our results warrant us in recommending that you give

serious consideration to the employing of renal angiography as one of your methods of evaluating the status of the upper urinary tract in patients with known, proven renal pain that you have been unable to explain. In this connection, I should like to call to your attention the fact that a pressor substance is produced in the congested kidney due to venous obstruction as well as in the ischemic kidney resulting from arterial compression and that hypertension can and does occur as the result of either of these two circumstances. This, of course, is an intriguing field for investigation and I am certain that angiography will be of use in its study.

I believe that our unselected series of over 1,500 cases is sufficiently large and covers a broad enough range of investigation to warrant our re-emphasizing that the procedure of translumbar arteriography, and the production of renal angiograms by it, is one whose employment carries with it dangers so slight that it can be used as a routine procedure.

In conclusion, I should like to state that the information to be derived from renal angiography provides us with data that allow a more accurate and scientific study of the upper urinary tract and, consequently, we can be more certain of the correctness of our diagnosis and prognosis and have a greater sense of security in the therapeutic advice that we give to patients.

*1714 Biscayne Blvd., Miami 32, Fla.*

## EXPERIENCES WITH HIGH CONCENTRATION UROKON FOR PYELOGRAPHY

REED M. NESBIT AND THOMAS E. NESBITT

*From the Department of Surgery, Section of Urology, University of Michigan Hospital,  
Ann Arbor, Mich.*

Two years ago we reported upon the clinical use of Urokon in over 1,000 cases and asserted the value as well as the safety of this compound in pyelography. Since that time many reports have substantiated our original observations.

In the early clinical investigations performed on this medium two concentrations were employed, 30 per cent and 50 per cent and it was noted that no important difference existed in the quality of pyelograms in the two groups. However, significantly fewer unpleasant reactions occurred when the lower concentration was employed. As the 30 per cent solution appeared optimal the commercial preparation was packaged in 25 cc ampules at that concentration. Urokon in this strength and amount produced no more than half the reactions than other compounds that were commercially available and yielded pyelograms which were at least as good in quality as the other media.<sup>1, 2</sup>

The manufacturer of Urokon, in an effort to reduce further the incidence of reactions, added a new stabilizing fraction. Our investigations with the newer preparation have indicated a lower occurrence of reactions in 356 instances where it has been used; 16 per cent reactions as compared to 19 per cent with the original Urokon 30 per cent.

More recently the manufacturer produced for investigational purposes a 70 per cent solution of the improved compound for use in angiography. A preliminary report of its use in urology was published by Wall and Rose in 1951.<sup>3</sup> Their main purpose was the production of nephrograms by taking roentgenograms a few seconds following the rapid administration of high concentration contrast medium. They discovered fortuitously that subsequent roentgenograms yielded pyelograms with superior quality and suggested "that present routine dosages for excretory pyelography do not provide the maximum amount of organic contrast medium that can be utilized to outline the collecting system."

Prior to the publication of their report, our own interest in the matter was stimulated following our utilization of 70 per cent Urokon for translumbar aortography. The concentrated Urokon has been found to be so free from untoward reactions in this connection that it is now injected under local anesthesia and sedation rather than general anesthesia. This permits the employment of stereoscopic and multiple injection techniques. The present method is to use 10 cc of 70 per cent Urokon per injection with immediate film development prior to subsequent injections. Up to 50 cc of 70 per cent Urokon in divided doses at one sitting without repositioning of the needle has been administered without un-

Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 20, 1952.

<sup>1</sup> Nesbit, R. M. and Lapidès, J.: Univ. Mich. Med. Bull., 16: 37, 1950.

<sup>2</sup> Nesbit, R. M. and Lapidès, J.: J. Urol., 63: 1109, 1950.

<sup>3</sup> Wall, B. and Rose, D. K.: J. Urol., 66: 305, 1951.

toward reactions. One patient with obstruction of the aorta just below the inferior mesenteric artery level mentioned a rather intense warm sensation of the lower extremities lasting 20-30 seconds but no other sequelae have been noted (fig. 1). The opacity of the entire arterial pattern obtained with 70 per cent Urokon appears to be superior to that seen with other contrast media. This may be explained by its molecular iodine content of 66.5 per cent compared to 49.8 per cent for Diodrast and 51.5 per cent for Neo-iopax.<sup>4</sup> In lieu of its demonstrated superior qualities, 70 per cent Urokon has more recently been utilized for angiocardiology in the University Hospital. Those concerned with its use in this connection report that they are impressed with its freedom from the rather profound reactions which they have previously observed when using other contrast media.



FIG. 1. Arteriography using 70 per cent Urokon demonstrates constriction of lumbar aorta.

Horger, Dotter and Steinberg of Cornell have reported electrocardiographic changes suggestive of myocardial ischemia and coronary insufficiency which occurred immediately following the rapid injection of 70 per cent Diodrast and 75 per cent Neo-iopax for angiocardiology.<sup>5</sup> These investigators have suggested this phenomenon as a possible explanation for deaths that have occurred following angiocardiology. They observed these changes to occur in the electrocardiograms of 5 out of 21 cases that were studied.

We have recently made continuous electrocardiographic tracings on 10 patients who were submitted to the same technique of angiography in which 50 cc of 70 per cent Urokon was administered in 3 to 5 seconds. In our cases the procedure was carried out for making nephrograms but the site and technique of

<sup>4</sup> Neuhaus, D. R., Christman, A. A. and Lewis, H. B.: *J. Lab. Clin. Med.*, 35: 43, 1950.

<sup>5</sup> Horger, E. L., Dotter, C. T. and Steinberg, I.: *Am. Heart J.*, 41: 651, 1951.

injection were identical to that described by Horger et al. for angiocardiology (fig. 2). Electrocardiographic tracings were made prior to the injection, with a continuous tracing made during the injection and for 1 minute following; serial tracings were also made at 1 minute intervals for a period of 10 minutes afterward. In no instance were demonstrable changes present indicative of any degree of coronary artery insufficiency or myocardial ischemia. Slight tachycardias were noted and minor changes due to vagal stimulation and respiratory alterations. Two patients exhibited one or two premature beats but no additional electrocardiographic abnormalities of significance.<sup>6</sup> Cardiologists appear to differ in their interpretations of the changes in the electrocardiographic tracings reported by the Cornell group and the present authors are in no position to enter that discussion for we are not cardiologists. However, if the absence of the changes in



FIG. 2. Nephrogram: Exposure of film a few seconds after intravenous injection 70 per cent Urokon.

question comprises a factor of safety then the observations which have been reported in respect to Urokon may be of significant importance.

Urokon 70 per cent has been used for pyelography in 585 consecutive patients including many individuals with marked impairment of renal function who ordinarily would not have been studied by excretory pyelography with the conventional dosages of contrast medium. The quality of the pyelograms was judged by the aggregate opinion of our daily pyelogram conference as has been the practice since the original investigations of Urokon began. The pyelograms are rated poor, fair, good and excellent. Poor quality films are those in which no satisfactory excretion of contrast medium occurs. Fair refers to a visible excretion but in which definite diagnosis other than obstructive uropathy cannot be established. Good refers to satisfactory pyelograms which enable definite opinion regarding diagnosis and excellent denotes a quality which is equal to that seen in satisfactory retrograde pyelograms (fig. 3).

<sup>6</sup> Stow, R. M., Figley, M. M. and Nesbitt, T. E.: Unpublished data.

Poor pyelograms were obtained in 7 per cent of the cases. It is interesting to note that each set of films classified as poor was made on patients with known diminution in total renal function who otherwise would not be considered a candidate for excretory pyelography. Many such patients in this series surprisingly were found to have satisfactory pyelograms as well. Fair quality pyelograms were observed in 14 per cent, and pyelograms of good or excellent quality were seen in 79 per cent of the cases. In one third of the cases the density of the pyelographic shadow was considered to be equal to that of retrograde pyelograms. No previous analysis with any other medium has ever approached these figures. See table 1.

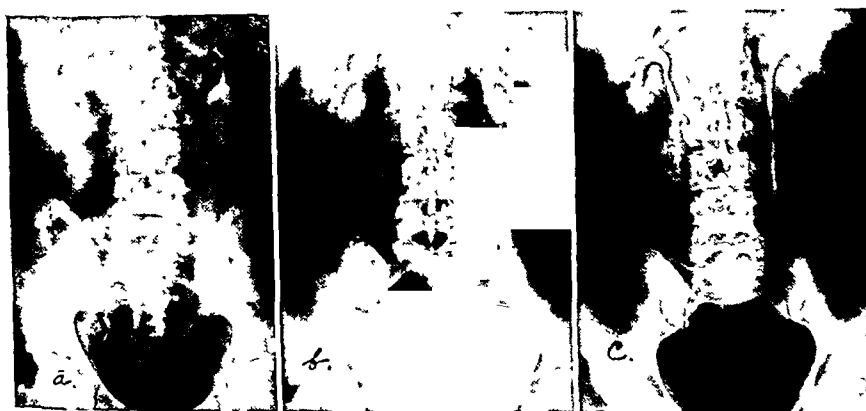


FIG. 3. Quality of excretory pyelograms made with 70 per cent Urokon. *a*, Fair. *b*, Good. *c*, Excellent.

TABLE 1. *Pyelogram quality*

|           | 30% UROKON<br>1000 CASES | 70% UROKON<br>582 CASES |
|-----------|--------------------------|-------------------------|
| Poor      | 11%                      | 7%                      |
| Fair      | 25%                      | 14%                     |
| Good      | 64%                      | 79% { 45%               |
| Excellent |                          |                         |

The pronounced advantage of Urokon 70 per cent is accompanied by various mildly annoying side reactions, the incidence of which is not importantly different from that encountered with other media except the 30 per cent Urokon, which is significantly lower. Reactions have been observed in 55 per cent of the cases. Over two thirds of the reactions consisted of transient flushing or nausea, either alone or combined, lasting 30 to 60 seconds. Allergic reactions consisting of sneezing, numbness of the lips, or urticaria occurred in 5.5 per cent (table 2). It has been observed that the immediate intravenous injection of 5 cc benadryl 10 mg./cc relieves these allergic reactions almost instantly. Experiments with prevention of the occurrence of the allergic reaction by premedication using pyribenzamine have not prevented the occurrence of this type of reaction. It has

been postulated by authorities in allergy that antihistamine drugs should not prevent these reactions, only relieve them when they have occurred. It has been believed that the tremendous improvement in pyelogram quality overshadows the objectionable features of these side reactions. We are now using Urokon 70 per cent exclusively for pyelography in the University Hospital. Twenty five cubic centimeters of the solution are injected into the arm vein, using a 20 gauge needle. The injection time is approximately 60 seconds. Slower rate of injection, up to 5 minutes, has been employed without any evident advantage.

TABLE 2. *Unpleasant reactions*

|                      | 30% UROKON<br>1000 CASES | 70% UROKON<br>585 CASES |
|----------------------|--------------------------|-------------------------|
| Total reactions..... | 18%                      | 55%                     |
| Flushing.....        | 0%                       | 19%                     |
| Nausea.....          | 12%                      | 19%                     |
| Vomiting.....        | 4%                       | 5%                      |
| Arm pain.....        | 2%                       | 2%                      |
| Taste.....           | 1%                       | 2½%                     |
| Urticaria.....       | 1%                       | 5½%                     |
| Dizziness.....       | 0%                       | 1%                      |

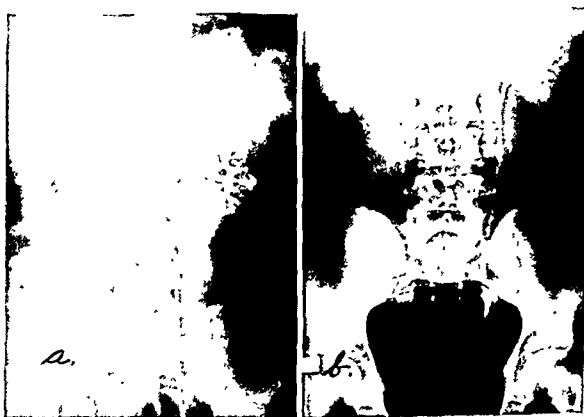


FIG. 4. Comparison of retrograde (a) and excretory pyelograms (b) in same subject.

Various studies are in progress to determine the clearance rates of Urokon excretion, and it has been determined that "good and excellent" pyelograms result when values of 40 to 85 mg. of iodine/ml. of urine are excreted. This compares favorably with the iodine concentration of retrograde media in routine use (fig. 4). Tests were made upon several patients who had retrograde pyelograms with 12½ per cent sodium iodide which is routinely used in our clinic. After injection of 5 to 6 cc of the solution, and ascertaining the location of the catheter tip within the renal pelvis by x-ray, the admixture of urine and contrast medium was allowed to flow out of the catheter and collected for analysis. This revealed values of 60 to 85 mg. of iodine/ml. of fluid.

The properties of 70 per cent Urokon which allow its excretion at these high concentration levels are not readily explained. Several interesting postulates enter into such a consideration, however, based on physiological aspects of renal function. Of primary importance is the realization that with the introduction of 25 cc of a 70 per cent solution 17.5 gm. of Urokon containing 11.6 gm. iodine is rapidly dispersed throughout the circulatory system. This produces extremely high blood levels of iodine and it has been generally assumed that Tm (maximum tubular excretory capacity) is reached at much lower levels. With the higher blood levels, then, the fraction of iodine removed from the plasma and filtered into the collecting system by the glomerulus becomes of increasing importance, possibly even resulting in an equivalent or greater amount of iodine appearing in the tubule from glomerular filtration than from tubular excretion. An additional factor possibly influencing this situation would be a diminished protein-binding capacity of Urokon allowing a greater proportion of free circulating Urokon and resulting in increased diffusibility. This set of circumstances would establish a higher excretory load lending itself to more rapid excretion which in turn serves as a partial explanation for earlier appearance of satisfactory pyelograms with Urokon.

It appears evident that Urokon 70 per cent can be administered intravenously for pyelography as well as angiography with safety. The incidence of mildly annoying reactions is greater than occurs when 30 per cent Urokon is used but this feature is greatly overbalanced by the outstanding advantages inherent in the higher concentrated solution.



## A STUDY OF THE RADIATION HAZARD IN UROLOGY

ROBERT B. NAGLE AND EDWARD L. PEIRSON

*From the Urological Service of the Salem Hospital, Salem, Mass.*

It is well known that the ionizing effect of roentgen rays causes severe local tissue destruction under certain conditions, but the more insidious effects of total body radiation by repeated small doses are less frequently realized. Among these are depression of the hematopoietic and gonadal systems and the increase in incidence of malignant tumors. Although the radiation hazard in most departments of radiology is kept to a minimum by careful observance of protective measures, many urologists give little thought to this hazard and customarily sit at the foot of the cystoscopy table while x-ray exposures are being made.

We began to inquire into the degree of danger involved in urological x-ray procedures after crude tests seemed to indicate that an old tube in use at the time presented an excessive radiation hazard. Hunter, et al.<sup>1, 2</sup> have demonstrated that the hazard from secondary radiation is much greater than was formerly supposed. The urologist doing retrograde pyelograms is exposed not only to some degree of direct radiation but also to a proportionately greater degree of secondary radiation from the body of the patient, the table, and the throat of the tube. Hunter further demonstrated that dental type x-ray film provided an accurate and convenient measuring device for radiation monitoring. The theoretical considerations and methods involved are completely described in the second of his two papers and by DeAmicis, et al.<sup>3</sup> Suffice it to say that the individual being monitored wears a small metal badge containing a dental type x-ray film, covered in part with graduated metal filters. After exposure for a given period (usually a week or two), these films are developed and compared with standards, and the degree of exposure calculated. This service is available commercially and is quite inexpensive.

We believed that the problem consisted of two parts: first, is the busy urologist exposed to hazardous levels of x-radiation when using modern equipment; and second, if so, what protective measures are available? We therefore began evaluating the degree of exposure and available protective measures by use of the film badge method.

We believe that to be practical any protective measure must meet certain requirements: first, it must confer a significant degree of protection; second, it must permit the urologist to remain quite close to his operating position; third, it must not be so cumbersome, inconvenient, nor uncomfortable as to discourage its habitual use. Cubicles, lead aprons, lead curtains, and the like cannot meet these requirements.

Accepted for publication September 25, 1952.

<sup>1</sup> Hunter, F. I., Merrill, O. E., Trump, J. G. and Robbins, L. L.: Protection of personnel engaged in roentgenology and radiology. *New Eng. J. Med.* **241**: 79-89, 1949.

<sup>2</sup> Hunter, F. I. and Robbins, L. L.: The protection of personnel engaged in roentgenology and radiology: Final report. *New Eng. J. Med.*, **244**: 9-13, 1952.

<sup>3</sup> DeAmicis, E., Spalding, C. K. and Cowing, R. F.: Survey of x-ray exposures in hospital personnel. *J. A. M. A.*, **149**: 924-926, 1952.

Since the intensity of the radiation is inversely proportional to the square of the distance from its source, movement away from the table offers one ready means of protection. Depending upon the distances and circumstances involved, this might or might not be feasible. The use of a cone on the x-ray tube is another obvious method of limiting both direct and secondary radiation. However the usual round cone is inconvenient and passes more radiation than is needed to expose the rectangular film. We therefore fitted into the throat of our tube a lead plate with a rectangular opening of a size which limited direct radiation to the exact pattern required to cover the plate (fig. 1). On theoretical grounds the use of a shield of this sort should improve the technical quality of the film. Since these means of protection (movement away from the table and limiting the

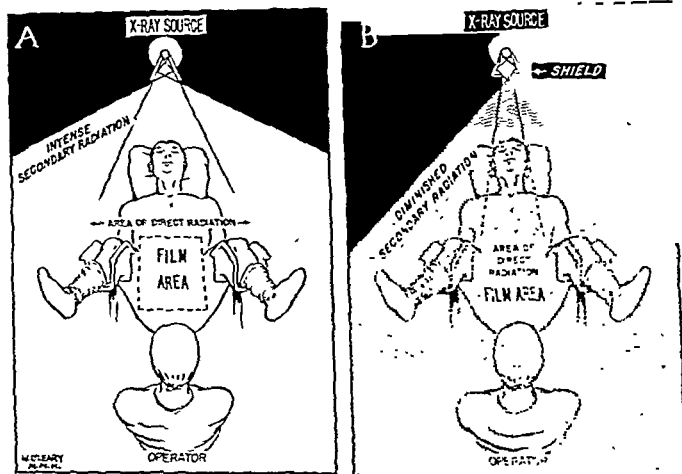


FIG. 1. A, diagrammatic representation of effects of unshielded tube. B, diagrammatic representation of effects of shielded tube.

x-ray beam by a shield) seemed to hold promise, it was decided to test them using the film badge method.

#### METHODS

For a period of ten weeks commercial film badges\* were placed in fixed positions during each retrograde pyelogram which was made in the Salem Hospital. Badge No. 1 was placed on the edge of the sliding drain pan of the cystoscopy table, which was withdrawn ten inches from the edge of the table. We took this as the approximate position of a urologist sitting at the foot of the table. Badge No. 2 was placed 18 inches beyond badge No. 1, and badge No. 3 was placed 18 inches behind badge No. 2. The lead shield was used during alternate weeks and the degree of exposure computed weekly. A record of the number of examinations, and the number of films taken was kept for each weekly period; and the results were tabulated to show the exposure expressed in milliroentgens per week in each of the three positions. Personnel moved from the vicinity of the

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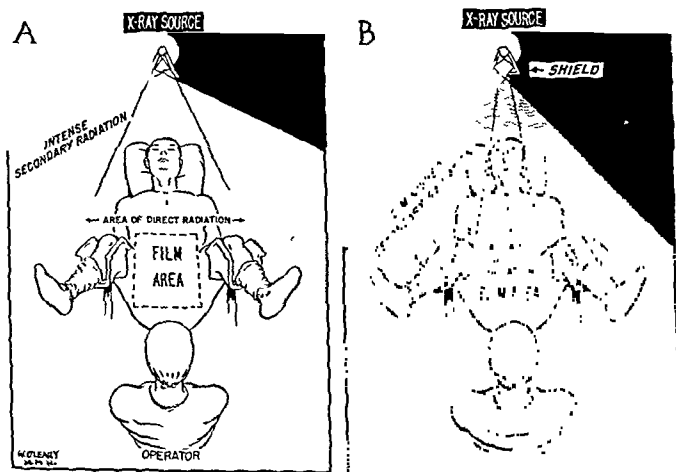


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badges during exposures. The x-ray equipment used was a 200 milliamperere Westinghouse full wave, valve tube rectification, rotating anode tube with a focal-film distance of thirty-six inches. Filtration was equivalent to 0.5 mm. of aluminum. The data obtained are summarized in tables 1 and 2. A shorter but similar experiment was carried out in another hospital, using General Electric x-ray equipment, and the results were quite similar to those obtained in the Salem Hospital.

TABLE 1. *Average weekly exposures expressed in milliroentgens. (Maximum Permissible Exposure 300 mr)*

|                                    | WITHOUT SHIELD | WITH SHIELD |
|------------------------------------|----------------|-------------|
| Badge 1, 10 inches from table..... | 278            | 76          |
| Badge 2, 28 inches from table..... | 64             | 40          |
| Badge 3, 46 inches from table..... | 40             | 26          |

Average weekly number of cystoscopies with pyelograms 7.4.

TABLE 2. *Average exposure per cystoscopy and per x-ray film*

|              | WITHOUT SHIELD |         | WITH SHIELD |         |
|--------------|----------------|---------|-------------|---------|
|              | mr/cyst.       | mr/film | mr/cyst.    | mr/film |
| Badge 1..... | 33             | 11      | 12          | 3       |
| Badge 2..... | 8              | 3       | 6           | 2       |
| Badge 3..... | 5              | 1       | 4           | 1       |

#### DISCUSSION

The exposure for the weekly periods was quite consistent. It will be seen that during our average week of 7.4 series of retrograde pyelograms, the urologist sitting at the foot of the table in the usual position received 278 milliroentgens of radiation when using the unshielded tube. Subcommittee No. 1 of the Advisory Committee on X-ray and Radium Protection gives the permissible dosage rate per week as 300 milliroentgens, which leaves a rather small margin of safety. Certainly, a urologist in a busy clinic might easily exceed this level.

However, 18 inches back of this position there is a marked decrease in exposure to an average value of only 64 milliroentgens. Moving back another eighteen inches does not give a proportionate decrease. By contrast, use of the lead shield reduced the exposure at the foot of the table to an average value of 76 milliroentgens per week, or only 27 per cent of the value for the unprotected tube. With the use of the shielded tube, there was a definite but less marked decrease in exposure with increasing distance from the table.

From these data it will be seen that if the urologist is willing to move a very short distance away from the table while exposures are being made, he can achieve an adequate degree of protection against radiation. By cutting the size of the x-ray beam to the exact size required, a urologist who does less than 25 pyelograms a week will not exceed the permissible level even if remaining seated at the table.

## CONCLUSIONS

Radiation hazard should be carefully checked, especially in installations using old or poorly protected equipment.

With modern equipment the urologist who does seven to ten retrograde pyelogram series per week risks overexposure to x-radiation if no protective measures are taken.

The urologist can reduce exposure to a permissible level by stepping back a short distance from the foot of the table during exposures.

The same protection can be obtained by limiting the size of the x-ray beam to the minimum required to cover the film by the use of an accurately cut metal shield mounted in the throat of the tube.

*374 Essex St., Salem, Mass.*

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### SECTION MEETINGS

*Northeastern Section*, Shawnee Inn, Shawnee on Delaware, Pa., September 15-18, 1953  
*South Central Section*, Hotel Muehlebach, Kansas City, Mo., September 21-23, 1953  
*North Central Section*, Cincinnati, O., October 8-10, 1953  
*Southeastern Section*, Whitehall Hotel, Palm Beach, Fla., April 12-15, 1954

The members of the executive committees of the various Sections and the list of officers and members of the executive committees of the Branch Societies will be found on pp. 856-858, June 1953 issue

## SURGICAL AND HORMONAL THERAPY OF BENIGN AND MALIGNANT ANDROGENIC HYPERFUNCTION OF THE ADRENAL CORTEX

CLARENCE V. HODGES

*From the Department of Surgery, University of Oregon Medical School, Portland, Ore.*

The management of the adrenogenital syndrome presents an intriguing surgical and endocrinologic problem. Selye's elaboration of the alarm reaction and the adaptation syndrome, the isolation of various fractions associated with adrenal cortical activity and the development of diagnostic tools for estimation of its functions constitute far-reaching contributions toward present understanding of this particular phase of adrenal cortical hyperfunction. The purpose of this presentation is to contrast the efficacy of surgical and hormonal methods of controlling benign overactivity of the adrenal cortex in the adrenogenital syndrome, to present an attempt to suppress this syndrome in a patient exhibiting metastases from an adrenocortical carcinoma and to point out a means of differentiation between benign and malignant adrenocortical hyperplasia.

The most frequently encountered example of the adrenogenital syndrome in childhood is the female pseudohermaphrodite. The enlarged clitoris and prominent labial swellings raise immediate doubt as to the sex of the patient. Varying degrees of abnormality of the urethra and vagina are found, the commonest being a persistent urogenital sinus with absence of the normal vaginal opening. Progressive virilization occurs with early appearance of pubic hair, acne, somatic overgrowth and advanced bone and height age. The presence of virilizing changes at birth is good evidence that the condition is due to congenital adrenal hyperplasia rather than to adrenal tumor, although adrenal cortical tumors have been reported during the first few months of life. Female pseudohermaphrodites are constitutionally rugged, are excellent surgical risks and show little tendency to Addisonian crises.

The adrenogenital syndrome in male children (macrogenitosomia precox) may be caused by either adrenocortical hyperplasia or adrenal tumor. Unlike females, these patients with adrenocortical hyperplasia tend to exhibit episodes of acute adrenal insufficiency and may not survive long enough to allow genital changes to occur or the condition to be suspected. Rapid virilization occurs; hypertension has been reported infrequently.

The total urinary excretion of 17-ketosteroids is markedly increased in the adrenogenital syndrome caused by either hyperplasia or tumor of the adrenal cortex. This finding serves to differentiate adrenal cortical hyperfunction from intersexuality, but this condition is best ruled out by exploratory laparotomy and biopsy of the gonads. In instances of sexual precocity, 17-ketosteroid excretion is within normal adolescent or adult levels (Wilkins).

Surgical procedures that have been utilized in the adrenogenital syndrome may be categorized as: 1) exploratory laparotomy to determine the patient's sex;

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 20, 1952.



2) adrenal exploration for removal of tumor or partial or complete extirpation of hyperfunctioning glands; 3) adjunctive procedures, such as amputation of the clitoris and plastic operations on the urethra or vagina.

Broster et al. reported little benefit from unilateral total adrenalectomy in pseudohermaphroditism. H. H. Young described techniques for bilateral simultaneous adrenal exposure and plastic procedures on the clitoris and vagina and cited good results after bilateral partial adrenalectomy. Lewis, Klein and Wilkins described the results of bilateral total adrenalectomy.

Wilkins et al. described the suppression of elevated urinary 17-ketosteroid excretion in a female pseudohermaphrodite treated with cortisone and later reported cases in which there was suggestive evidence that virilization had been checked; similar depression of 17-ketosteroids was reported by Bartter et al. Scardino and Prince cited a case with similar results and improvement in personality. Shepard and Clausen found not only suppression of abnormal 17-ketosteroid excretion but also relief of concomitant hypertension (as in one of Wilkins' cases) after administration of cortisone. These authors forecast portions of the present study (pertinent details had been carried out when their report was published) when they wrote, "Will the 17-ketosteroids be reduced when cortisone is given to patients with adrenal tumors? A short course of cortisone may possibly aid in making a differentiation between tumor and benign hyperplasia."

#### CASE REPORTS

Four female patients exhibiting the adrenogenital syndrome are included in the present series. In 3 instances, congenital adrenocortical hyperplasia was found; the fourth patient was shown to have a carcinoma of the adrenal cortex. Their ages when first seen ranged from 5 days to 7 years.

*Case 1.* A. B., No. 157195, a white female child of  $7\frac{3}{12}$  years, entered the University of Oregon Medical School Hospitals on July 6, 1950, as a "hermaphrodite." She had grown rapidly since birth and was 4 inches taller than her 10 year old normal sister. Pubic hair had appeared at 3 years. Physical examination revealed a slender, awkward child whose height was  $58\frac{1}{2}$  inches (average normal 47.9 inches), weight 77 pounds (average normal 49.5 pounds). The peripheral blood pressure was 100/65. Abnormal findings were abundant pubic hair and an enlarged clitoris measuring 2 cm. in length and 1 cm. in diameter (fig. 1, A). The urethral and vaginal openings were separate and normally placed. Vaginoscopy disclosed a normal cervix; the uterus was palpable on recto-abdominal examination under anesthesia. Cystoscopy, excretory and retrograde urography, and laminographic studies of the adrenal regions revealed no abnormality. The bone age was 10 years. All laboratory studies were normal; 17-ketosteroid determinations were not available.

Nine days after admission, adrenal exploration was carried out through bilateral vertical lumbar incisions (fig. 1, B), the classical procedure of Young being modified only to the extent that a 3 cm. portion of each twelfth rib was resected near the angle of the rib to allow its retraction upward and facilitate exposure. Both adrenals were large but were otherwise normal. Portions of each

adrenal gland, approximating  $\frac{3}{8}$  of the left and  $\frac{5}{8}$  of the right, were removed. The postoperative course was uneventful and the patient was discharged on the twelfth day. The pathological report indicated normal adrenal tissue.

The patient was re-admitted on August 6, 1951. She had grown 3 inches during the previous 13 months and was otherwise unimproved by her adrenal resections. Amputation of the clitoris was necessitated by the psychic stress imposed by her unusual appearance (fig. 1, C). Total 17-ketosteroid excretions at this time were 14.6, 15.0 and 15.3 mg./24 hours. She was re-admitted on March 12, 1952, having grown  $1\frac{3}{4}$  inches and gained 8 pounds in the interim of 7 months. Early breast

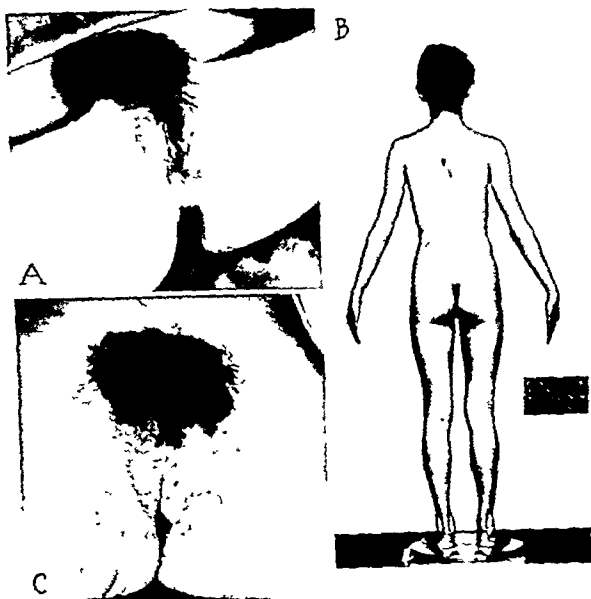


FIG. 1. Case 1. A) hypertrophied clitoris and labia, abundant pubic hair. Urethral and vaginal orifices normally situated. C) after clitoridectomy. B) operative site, bilateral simultaneous lumbar exposure of adrenal glands.

development was apparent. The bone age was  $13\frac{1}{2}$  years (chronological age  $9\frac{1}{2}$  years). 17-ketosteroid determinations showed 27.8 and 24.8 mg./24 hours.

Cortisone acetate, 100 mg. daily by mouth in 4 divided doses, was begun 3 days after admission and decreased after 5 days to a maintenance regimen of 25 mg. daily in 4 divided doses. 17-ketosteroid excretion (fig. 2) dropped to 10.6 mg./24 hours within 7 days (normal up to 2.5 mg. at this age) and has continued its trend toward normal ranges. The acne disappeared in 3 weeks. Further decreases in virilization have not been noted in the short period of observation since cortisone therapy was initiated; marked improvement in personality has been observed.

Case 2. M. T., No. 185312, a white girl, 5 days old, entered the University of Oregon Medical School Hospitals on July 12, 1950, for determination of sex. Gestation and birth were normal. Positive findings were enlarged labia majora and a clitoris, 1.5 cm. in length, with a hypospadiac external urethral meatus

at its base and a broad flat urethral groove extending distally along its ventral aspect. There was no vaginal opening. Testes could not be palpated. Rectal examination gave the impression of a small, normally situated uterus. Urethrography did not reveal a vaginal communication.

At 15 months, clitoral enlargement was more pronounced (fig. 3). Urethros-copy revealed a small, irregular vaginal opening at the junction of the middle

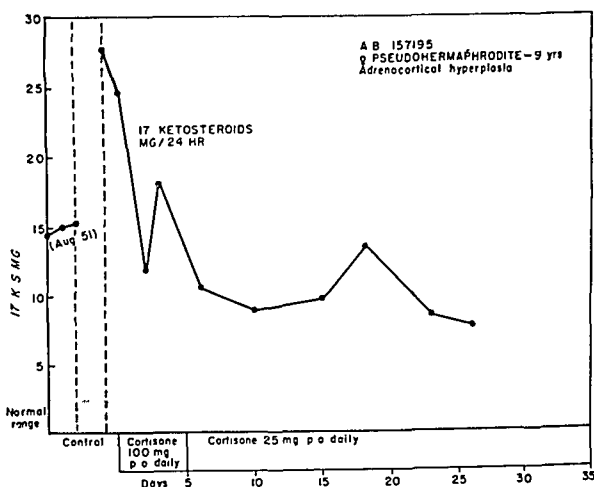


FIG. 2. Case 1. Marked suppression of 17-ketosteroid excretion by cortisone



FIG. 3. Case 2. External genitalia. Hypertrophied labia and clitoris, pubic hair, hypo-spadic urethra; persistent urogenital sinus.

and distal thirds of the urethra. A 4F ureteral catheter was passed into this opening a distance of 4 cm. Injection of 4 cc 40 per cent skioidan revealed a vaginal cavity of approximately normal size; there was no reflux into the cervical canal. Exploratory laparotomy disclosed a normal uterus and tubes, with attached gonadal tissue shown to be normal ovaries on biopsy. Palpation of the adrenal glands revealed no abnormality. The abdomen was closed and the clitoris amputated. Convalescence was uneventful. 17-ketosteroid values were 14.4 and 17 mg./24 hours (normal range less than 0.8 mg.).

Upon re-admission at 25 months, moderate acne and fine pubic hair were noted.

The height was  $38\frac{3}{4}$  inches (average normal 33.4 inches), weight 34 pounds (average normal 25.7 pounds). The peripheral blood pressure was 104/68. Pre-treatment 17-ketosteroid levels were 12.3, 15.9, and 11.5 mg./24 hours. Routine laboratory studies, including serum electrolytes, were normal. Cortisone acetate, 25 mg. intramuscularly daily, was given for 8 days, during which period excretion of 17-ketosteroids dropped to 1.5 mg./24 hours (fig. 4); cortisone was then decreased to 25 mg. every other day. A further decrease to 12.5 mg. intramuscularly every third day resulted in maintenance of 17-ketosteroid excretion at levels slightly higher than the normal range. The acne showed evidence of clearing during the third week of therapy but no change was noted in the pubic hair.

Case 3. B. S., No. 190400, a white girl of 6 years, entered the University of Oregon Medical School Hospitals on July 15, 1950, because of masculinization

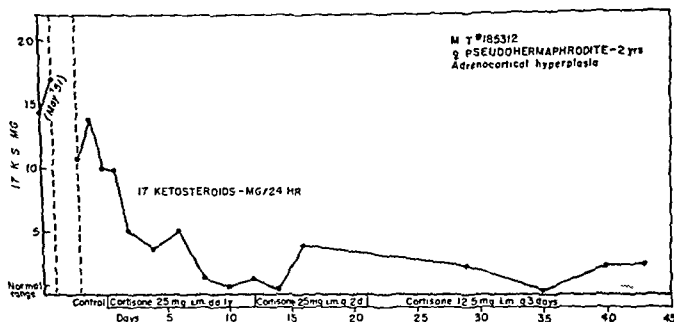


FIG. 4. Case 2. Marked suppression of 17-ketosteroid excretion by cortisone

and abnormal growth. Clitoral enlargement was noted at birth. Pubic hair appeared at 3 years and was followed by rapid growth and deepening of the voice. Body height was  $54\frac{1}{2}$  inches (average normal 44.6 inches), weight 68 pounds (average normal 42 pounds). The peripheral blood pressure was 114/60. There was abundant pubic hair with female distribution. The labia majora were large and wrinkled. The clitoris, 4 cm. long and 1.5 cm. in width, exhibited a hypospadiac deformity with a small urethral opening at its base. No vaginal introitus was present. No testes were palpated. Urethroscopy revealed no evidence of urethrovaginal communication. Cystoscopy and excretory urography revealed no abnormality. The bone age was 11 years. Exploratory laparotomy disclosed a normal uterus, tubes and ovaries (biopsy); palpation in the adrenal areas was unsatisfactory but did not suggest the presence of tumor. Adrenal exploration was carried out 14 days later in the manner described for case 1. Approximately one-half of each hyperplastic adrenal gland was removed. Convalescence was uneventful.

Re-admission 11 months later was occasioned by psychic problems concerned with the enlarged clitoris. The height was 57 inches, weight  $74\frac{1}{2}$  pounds. Although it appeared that the growth rate had been decreased somewhat by hemi-adrenalectomy, virilization was as pronounced as before. Acne was noted across the shoulders. Routine laboratory studies were normal. The daily 17-

ketosteroid excretion determinations were 15.2, 23.6 and 38 mg. Clitoridectomy was carried out. Cortisone therapy is contemplated but has not, as yet, been instituted.

*Case 4.* J. C., No. 191146, a white girl of 3 years, entered the University of Oregon Medical School Hospitals on August 23, 1950, because of rapid growth, appearance of pubic hair, enlargement of the clitoris of 1 month's duration and discovery of a left upper abdominal mass 10 days previously. The patient appeared approximately 2 years older than the stated age. Body weight was 41 pounds. The peripheral blood pressure was 128/100. A hard, slightly tender, somewhat nodular mass occupied the entire left upper quadrant of the abdomen, producing a visible bulge (fig. 5, *A*). A small amount of pubic hair was noted



FIG. 5. Case 4. *A*, left upper quadrant mass, pubic hair, hypertrophied labia and clitoris *B*, left retrograde pyelogram; normal left kidney displaced inferiorly by large adrenal tumor.

along with hypertrophy of the clitoris and labia majora. Separate urethral and vaginal openings were present. The bone age was 10 years. The chest x-ray was negative. Vaginoscopy revealed a normal vagina and cervix. Retrograde pyelography showed a normal left kidney with marked downward displacement (on rectal examination the lower pole of the left kidney was palpable at the tip of the examining finger!) due to an overlying mass (fig. 5, *B*). Routine laboratory studies were normal except for mild anemia.

Six days after admission, a large left adrenal tumor was removed through a transverse upper abdominal, transperitoneal approach. This incision provided excellent exposure and, after the posterior parietal peritoneum had been incised lateral to the splenic flexure of the colon, easy access to the blood supply of the mass before mobilization was attempted. Since the left renal vessels crossed the lower pole of the tumor, sacrifice of these vessels and removal of the normal left kidney was necessitated. Separation of the tumor by blunt and sharp dissection was easily accomplished but, in freeing the upper pole, a small rent was made in its extremely thin wall and small pieces of grayish-red, friable tissue

were extruded. The procedure was completed without incident; convalescence was rapid and uneventful. The tumor measured 15 by 9 by 9 cm. and weighed 770 gm. Pathologic study revealed an adenocarcinoma of the adrenal cortex with focal hemorrhages, necrosis and invasion of vascular channels.

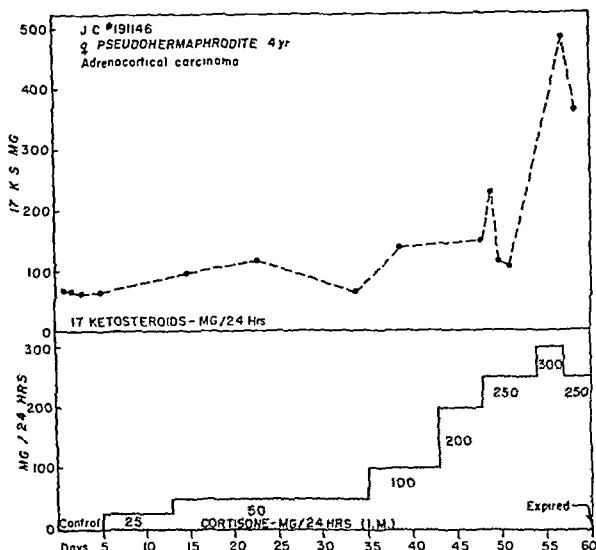


FIG. 6. Case 4. 17-ketosteroid excretion increased rapidly until death; cortisone therapy, ranging from small to massive doses, completely ineffective.



FIG. 7. Case 4. Far advanced pulmonary metastases from adrenocortical carcinoma

The patient grew 2 inches and gained  $4\frac{1}{2}$  pounds in the immediate post-operative period of 4 months. Pubic hair, after temporary thinning, became more prominent; the voice deepened. No change was noted in the clitoris. Multiple pulmonary metastases were evident radiographically at 8 months. The patient was re-admitted for cortisone therapy 13 months after surgery.

Control studies of total urinary 17-ketosteroid excretion averaged 66 mg./24

hours. Cortisone acetate, 25 mg. daily intramuscularly, was begun on 10-1-51 and increased gradually over a period of 49 days to a peak of 300 mg. daily (fig. 6). Daily 17-ketosteroid excretion increased rapidly but with rather wide fluctuations to an extreme of 464 mg. 3 days before death. There was no evidence of clinical improvement to be credited to cortisone therapy. Pulmonary metastases increased in size and number (fig. 7); the unfavorable course progressed to apathy, dyspnea, coma and death on the fifty-fifth day after therapy was initiated. Side-effects noted were slight rounding of the face, elevation of the peripheral blood pressure to 144/118 and mild glycosuria. Autopsy revealed extensive pulmonary, cerebral, hepatic and retroperitoneal metastases.

#### DISCUSSION

Three instances (cases 1, 2, 3) of female pseudohermaphroditism due to congenital adrenal cortical hyperplasia, as evidenced by clitoral and labial hypertrophy at birth, early appearance of pubic hair and acne, somatic and osseous overgrowth, elevation of total urinary 17-ketosteroid excretion and proven by exploratory laparotomy and/or adrenal exploration, have been subjected to surgical (partial extirpation of the adrenal glands) or hormonal (cortisone acetate) therapy or a combination of these procedures in attempting to suppress excessive secretion of androgenic hormones.

Two patients (cases 1 and 3) derived little or no benefit from surgical removal of approximately one-half of the total adrenal mass in each case. Evidence of masculinization was persistent and progressive following surgery. Determination of the 17-ketosteroid excretion levels was valuable in demonstrating objectively the degree of androgenic hyperfunction.

Two patients (cases 1 and 2) showed prompt decreases in 17-ketosteroid excretion toward normal levels after institution of cortisone therapy. This change has been accompanied by disappearance of acne, which may be interpreted as early evidence of suppression of the hyperandrogenic state. The period of observation has not been sufficiently extensive to indicate whether or not complete control of all aspects of the adrenogenital syndrome can be achieved; it is anticipated, however, that therapy with cortisone will prove superior to any of the methods previously employed. No significant side-effects have been encountered thus far, other than transient hypopotassemia and muscle weakness in one patient (case 2) which responded promptly to reduction in cortisone dosage and oral administration of potassium salts.

Bartter et al. have suggested that the primary defect in the adrenogenital syndrome with benign adrenocortical hyperplasia is a relative deficiency of "sugar" hormone and postulate the following sequence: "1) lack of 'sugar' hormone, 2) failure of normal inhibition of ACTH, 3) increased output of ACTH, 4) resulting increase of adrenal androgen." Although this hypothesis has not been completely verified by demonstrating increased production of ACTH in this syndrome, it provides a logical explanation for the benefits gained from administration of cortisone.

The indication that benign adrenal cortical cells with androgenic hyper-

function were susceptible to suppression by hormonal means led naturally to the implication that malignant cells, originating in the same area and exhibiting the same androgenic properties, might also be vulnerable to similar influences. This hypothesis was not supported by our experience with case 4. Although cortisone dosages were increased up to massive levels (300 mg. daily), there was no clinical evidence of benefit nor was there any influence on the enormously increased excretion of 17-ketosteroids.

The foregoing observations indicate, however, that the contrasting responses to a brief period of cortisone administration constitute an important diagnostic test in differentiating benign and malignant hyperfunction in a patient exhibiting the adrenogenital syndrome and may obviate the necessity for adrenal exploration where the diagnosis is in doubt.

#### SUMMARY

Hormonal therapy with cortisone was more effective than surgical extirpation of portions of the adrenal glands in controlling the adrenogenital syndrome due to benign hyperplasia of the adrenal cortex. Elevated urinary 17-ketosteroids were promptly reduced toward normal levels.

Cortisone therapy was ineffective in attempting to suppress metastases from an adrenocortical carcinoma in a patient exhibiting the adrenogenital syndrome. Elevated urinary 17 ketosteroids were unaffected.

The contrasting effect of cortisone on urinary 17-ketosteroid excretion in benign versus malignant hyperfunction of the androgenic elements of the adrenal cortex may be used as a means of differentiation.

Steroid determinations were carried out under the supervision of Drs. Raymond Grondahl and John Newman of the Department of Pathology.

Cortisone for this study was generously provided through the courtesy of Drs. Leo Curtin and Elmer Alpert, Merck and Company, Rahway, N. J.

Helpful advice from Dr. Lawson Wilkins regarding treatment regimens was gratefully received.

Case 1 was referred by Dr. Carl Heller, case 2 by Dr. George Walliker, case 3 by Dr. Don Rice.

*University of Oregon Medical School, Portland 1, Ore.*

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## INFARCTS OF THE KIDNEY

JOHN S. FITZGERALD AND PATRICK S. MULLINS

Urologists have been showing an increasing interest in the medical diseases of the kidney. We can be of aid to the internist and he to us. The group of cases caused by sudden occlusion of the arterial supply of the kidney brings problems in diagnosis and treatment that are mutual. All too frequently the pathologist makes the initial diagnosis.

### INCIDENCE

After Traube<sup>1</sup> reported the first diagnosed case in 1856, many sporadic case reports appeared in the literature until Barney and Mintz<sup>2</sup> in 1933 presented 4 cases and reviewed 143 autopsy records in which renal infarction was reported. Most cases occurred between the ages of 30 and 50 years: 57.5 per cent were males: Eighty-three per cent were seen and treated by internists. Cardiac disease was present in 95 per cent. The diagnosis had not been made in any of these cases nor had a urologic study been made.

In 1940, Hoxie and Coggins studied 14,411 autopsy records and found 205 cases in which the diagnosis had been made clinically in only 2 cases. Of these, 90 per cent were admitted to the medical service, only four were admitted to the urological service. Definite cardiac lesions were found in 76 per cent. Healed infarcts occurred in 25 per cent. Rheumatic heart disease was present in 64, coronary occlusion with mural thrombi in 29, bacterial endocarditis in 20 and arteriosclerosis in 24.

Regan and Crabtree<sup>4</sup> reviewed the literature extensively and added 4 cases of their own. They grouped these cases culled from the literature into two groups: 1) Those reported on a basis of clinical and autopsy findings; 2) those based on clinical findings plus urologic examination. By this ingenious method they brought out clearly how important urological study is as an aid to diagnosis.

### PATHOLOGY

The classification of Regan and Crabtree is simple and useful: Arterial infarction; venous infarction; traumatic infarction.

This paper will be confined to arterial infarction as we have not encountered venous or traumatic infarction. Allen<sup>5</sup> states: "The acute ischemic infarct is characteristically wedge-shaped with the base of the triangle at the capsule, yellow to yellowish-gray, and usually with a hemorrhagic border. Several isolated infarcts occur in the same kidney or the individual infarcts may coalesce to the extent of being indistinguishable from cortical necrosis of the kidney."

Read at annual meeting, Northeastern Section, American Urological Association, aboard the S.S. Ocean Monarch, October 4-10, 1952.

<sup>1</sup> Traube, L.: *Über den Zusammenhang von Herz und Nierenkrankheit*. Berlin: A. Hirschwald, 1856, p. 77.

<sup>2</sup> Barney, J. D. and Mintz, E. R.: *J. A. M. A.*, 100: 1-6, 1933.

<sup>3</sup> Hoxie, H. J. and Coggins, C. B.: *Arch. Int. Med.*, 65: 587-594, 1940.

<sup>4</sup> Regan, F. C. and Crabtree, E. G.: *J. Urol.*, 59: 981-1018, 1948.

<sup>5</sup> Allen, A. C.: *The Kidney*. New York: Grune and Stratton, 1951, pp. 466-472.

"In the healed state, the infarcted area appears as a deeply depressed area with the capsule usually increased in thickness, highly vascularized, and strongly adherent to the capsule in the area of infarction. The altered appertaining artery leading to the area may be identified in many instances. The scar of the infarct may be irregularly calcified. Occasionally, the residuum of an infarct is cystic, secondary to liquefaction degeneration of the infarcted tissue in the early stage.

"The hemorrhagic infarct almost always takes the form of hemorrhagic necrosis of the entire kidney, such as occurs in the newborn, after thrombosis of the renal vein."

#### CASE REPORTS

J. R., a man aged 38, was admitted to the hospital November 28, 1946 complaining of severe pain in the abdomen over the area of the left kidney of 1 day's duration. He had had two previous admissions; the first 5 weeks prior for a disturbance in the blood supply of his legs. This cleared up and was aided enough by epidural blocks that he was discharged 8 days after admission. A week later he was re-admitted with epigastric distress and tarry stools. A workup revealed a chronic duodenal ulcer. The white blood count was elevated ranging from 15,400 to 24,850 on 5 examinations. For one day he had pain accompanied by rigidity of the right rectus of such degree that perforation of the ulcer was considered, but surgery was never performed as the symptoms ameliorated during the period of observation. The general course showed enough improvement on an ulcer regimen to warrant discharge 21 days after admission.

Four days later the left renal pain occurred. This was severe without much radiation. There was tenderness of considerable degree in the left costovertebral angle. The urine revealed 1 plus albumin, 5 red blood cells and an occasional white blood cell per high power field. The excretory urogram was of interest. The right side was entirely normal. The left filled well but the lower half and lowest calyx presented a narrowing that amounted to just a thin line of the dye. A retrograde pyelogram performed by gravity duplicated this. The kidney pelvis was distended under pressure and the lower half filled quite normally. On the emptying picture the narrow line reappeared. The cause of this phenomenon is still unexplained. Culture and stained smear of the urine were negative.

A diagnosis of multiple infarcts of the kidney was made and nephrectomy performed without incident. The kidney was normal in size; many old and recent infarcts or abscesses studded the surface. No frank pus was noted on cross section. The microscopic study revealed small microscopic abscesses which seemed to be passing up collecting tubules.

The clinical course was smooth and the patient was discharged 10 days post-operatively only to be re-admitted a month later in respiratory distress with rapid, soft pulse. Despite supportive therapy he expired 6 days later. This, in all, was 5 weeks after the nephrectomy.

The postmortem examination revealed a pulmonary embolus. The auricular appendages contained some old partially organized thrombi. The duodenal

ulcer was healed with a good deal of fibrosis and adherent to the pancreas. Scattered throughout the right kidney were multiple thrombi with hemorrhagic infarcts. The spleen revealed an old infarct.

If we reconstruct the picture with the aid of the autopsy it is logical to assume that an infarct of the right kidney occurred on the earlier admission and was suspected to be a perforated ulcer. The left nephrectomy accomplished no useful purpose and further weakened the patient's reserve.

A. A., a woman, aged 49, was admitted April 1, 1947, acutely and seriously ill. She had severe pain in the abdomen and the left side of the back. The admitting diagnosis was rheumatic heart disease with failure. The pulse was 110, regular. The heart was enlarged to twice its normal size. A loud systolic murmur was heard over the entire precordium. The electrocardiograph revealed advanced myocardial damage with pericarditis.

There had been 4 previous admissions for rheumatic heart disease. One year prior to the present admission she had a urologic study performed by another urologist. The excretory urogram showed reduced flow in each kidney, otherwise normal. The retrograde pyelogram showed a slight enlargement of the right kidney pelvis and blunting of the calyces.

She was seen by us the day after admission. The pain had been sudden in onset radiating down the left side in characteristic renal distribution. It was accompanied by vomiting. Upon examination a well developed and well nourished seriously ill female was noted. She was cyanotic, dehydrated and toxic. The left kidney was tender but not palpable. Tenderness was present over the liver and over the left lower quadrant in a lessened degree.

The urine was dark amber, 1.015, 2 plus albumin, no sugar, 2 plus acetone, occasional red blood cells and 10 white blood cells per high power field and many hyaline and granular casts. A leukocytosis of 16,800 was present of which 14 were non-segmented, 74 segmented, lymphocytes 12. The hemoglobin was 84 per cent with 4,420,000 red blood cells.

The excretory urogram revealed faint visualization on the right, but none on the left. A cystoscopy was performed. The left ureteral orifice was swollen, the right normal. Drip was slow from each kidney. Culture was negative. The right pyelogram revealed slight hydronephrosis and blunting of the calyces. The superior calyx on the left side was cut off and the kidney depressed. Renal excursion was reduced on the left, normal on the right.

For 3 days following cystoscopy the patient showed definite improvement with lessening of the pain and tenderness and the vomiting. On the following day she went into complete collapse which required emergency treatment. The course here was progressively downhill. Icterus developed and became very marked terminally. She expired 21 days following the onset of symptoms.

The postmortem examination revealed marked evidence of rheumatic heart disease. In the thoracic part of the aorta were a few athermatous streaks and plaques but this was only of moderate degree. In the abdominal aorta the lumen was completely occluded by a thrombus which extended from a point about 3

cm. below the renal arteries down to the bifurcation of the aorta. The left common iliac artery was patent. The thrombus on the right side extended down through the common iliac into the external iliac and femoral arteries and extended beyond the point of resection. In the abdominal aorta the thrombus was red to brown and quite soft but was moderately adherent. In the right common iliac there were areas in the thrombus which were soft and almost fluid. In the distal part of the iliac artery and in the femoral artery the thrombus became pale, narrow and almost threadlike, having a diameter of only 0.2 cm. The lumen at this point was quite narrow and there was apparently no space for blood flow here. The threadlike thrombus was moderately adherent on the one side. The thrombus did not extend into the hypogastric artery.

The left renal artery was completely occluded by a dark red thrombus for a distance of 2 cm. along its course extending proximally from the junction of the artery with the kidney. The capsule stripped easily revealing an extensive infarct of the kidney extending primarily from the upper pole but continuing down the outer border on the anterior and posterior surface. The dimensions of this infarct were approximately 10 by 6 cm. and extended through the full thickness of the kidney. Its color was a deep red to light brown and in some areas was almost a canary yellow. The consistency was soft and doughy. No lesion was seen of the calyces, pelvis or ureters. The right kidney was somewhat smaller than usual. Near the midpoint of its convex or lateral surface was a deep scar which was 5 cm. long, 1.3 cm. wide and 0.6 cm. deep. This scar has a pale, rather granular base and almost divided the kidney into two parts. A similar smaller scar was present on the anterior surface and measured 1.8 by 1 by 0.6 cm. Sections showed these scars to have a base of gray firm fibrous tissue. The intervening kidney was quite smooth and showed no obvious lesion in any part. The pelvis divided into two equal parts and a separate ureter came from each part. This pelvis division was only superficial or partial and did not constitute a double kidney. The two ureters extended halfway to the bladder.

Section of the infarct in the left kidney showed complete necrosis with only faint skeletal outlines. There was a narrow zone of intact but congested parenchyma at the apex of one pyramid. Adjacent parenchyma showed marked congestion but there was no periphery of leukocytes.

Microscopic study of the right kidney showed that the scar had a center of hyalinized connective tissue and a periphery of very scarred kidney parenchyma containing partially or completely hyalinized glomeruli and scarred very atrophic tubules. The area was heavily infiltrated by lymphocytes. Adjacent kidney showed marked congestion and several areas heavily infiltrated by lymphocytes and contained scarred glomeruli and atrophic scarred tubules.

The thrombosis in the aorta was interpreted as occurring later than the renal infarcts, most likely at the time when the collapse occurred. The kidneys showed the scar of old infarcts as well as the current one.

This patient's condition was so critical that surgery was never feasible if indicated.

## DIAGNOSIS

Infarcts of the kidney occur usually in cardiac patients. A case of known heart disease should alert the urologist. Concomitant signs often predominate and infarcts are only part of the picture in many instances.

Pain is the outstanding symptom. It is sudden in onset, severe and prostrating. It is localized to the kidney region, being most marked in the costovertebral angle and upper quadrant of the same side. It is interesting to note in most of the reported cases, that pain is referred to the thigh, if referred at all. The pain lessens daily and usually subsides in 7 to 10 days. Localized tenderness and loin rigidity are marked at the onset and gradually disappear.

Temperature elevation is slight in sterile ischemic infarcts, high and oscillating in septic ones.

Leukocytosis is the rule. In our cases it varied from 12,000 to 25,000.

Albuminuria of moderate degree is a persistent sign both in our cases and those reviewed in the literature.

Microscopic hematuria is usual. The lack of gross hematuria was surprising. In venous thrombosis it is severe.

The excretory urogram is the most useful single aid. Visualization on the normal side with absence of function on the involved side is strong evidence of infarction. As healing occurs, function returns and will be recorded on the excretory urogram.

At cystoscopy failure of the function tests is confirmed. Urine culture is usually sterile. A normal pyelogram without obstructive signs with nonvisualization on the excretory urogram is very strong evidence.

Aortography has not been used. It is usually unnecessary but should be of great help in certain instances. Parke Smith<sup>6</sup> has demonstrated that an infarct can be diagnosed accurately by the characteristic sudden termination of arteries in region of infarcts with an area of avascularity between their termination and the renal capsule. Cedermarck et al.<sup>7</sup> used the procedure to diagnose an obscure case of total infarction months after it occurred and was able to give relief by nephrectomy.

We have not encountered hypertension as a result of this condition.

In our cases the differential diagnosis was confused with renal calculus, acute cholecystitis, perinephric abscess, perforated ulcer, and mesenteric thrombosis.

## TREATMENT

The majority of these cases are best treated symptomatically with primary attention to the underlying cardiac condition. Often the poor condition of the patient demands this. Even a total infarction, if sterile, heals by autonephrectomy. The possibility of another lesion occurring in the opposite kidney demands conservation of all renal tissue that remains. The accompanying and underlying pathology renders a grave prognosis regardless of the fate of the renal infarct.

<sup>6</sup> Smith, P. G., Rush, T. W. and Evans, A. T.: *J. Urol.*, **66**: 145-152, 1951.

<sup>7</sup> Cedermarck, J., Lindblom, K. and Herschen, F.: *Nord. Med. (Hygiea)*, **10**: 1793-1795, 1941.

Surgery, which is almost invariably nephrectomy, is indicated for septic infarcts and venous thrombosis. If hypertension develops, or persistent and unrelieved pain occurs, re-evaluation is necessary and surgery probably indicated.

#### SUMMARY

Two cases of infarct of the kidney have been presented along with a review of the literature.

Diagnosis is facilitated by urologic study.

Treatment is usually conservative and expectant.

It is the opinion of the authors that the lesion occurs more frequently than is diagnosed.

*264 Genesee St., Utica 2, N. Y.*

## CALYCEAL DIVERTICULA OR PYELOGENIC CYSTS

ROLLIN G. WYRENS

A recent discussion with some of my urologic colleagues brought out the fact that calyceal diverticula or pyelogenic cysts are generally little understood and to some they appear to be a totally unfamiliar entity. One urologist admitted that he had never heard of them, but on observing illustrative roentgenograms, remembered having seen similar lesions which he did not understand. I wonder if this may not be the experience of others?

One hundred years ago, Rayer described and called the condition "Kystes Urinaires." Very few reports have appeared subsequently in the literature. The terminology of this and related entities has been confusing. A calyceal diverticulum or pyelogenic cyst is an epithelial lined cavity in the kidney situated peripheral to a calyx and connected to it by a narrow isthmus. The epithelial lining is continuous with that of the calyx. They have been termed, correctly or incorrectly, calyceal diverticula, pyelogenic cysts, cysts urinaries, partial hydro-nephrosis, encysted calculus, intrarenal cyst, hydrocalycosis, calyceal or renal pocket and others. They have been erroneously called hydrocalycosis. Hydrocalycosis infers dilatation of a renal calyx secondary to obstruction of its infundibulum. In case of calyceal diverticula, except for a small communication with the diverticulum, the calyx otherwise is normal except in cases of concomitant calyceal disease.

In 1932 Damm first termed this lesion pyelogenic cyst. In 1941 Prather used the term calyceal diverticulum and pointed out that transitional epithelium, similar to the lining of the calyces, lined these areas. This is in contradistinction to the single layer of flattened cuboidal cell lining found in solitary cysts. This differential point cannot be made in all cases. Weyrauch and Fleming described a hydrocalyx with epithelium thinned to a one, cuboidal cell layer. This could conceivably happen to calyceal diverticula.

Though not absolutely proved, these diverticula are probably congenital in origin. One must consider the possibility of acquired cavities being formed and epithelialized when abscesses or hematomas empty into the calyceal system. Many authors differentiate these diverticula from renal cysts that rupture into a calyx and attempt pathologic differentiation by a study of the epithelial lining. Foley, in a discussion of a paper by Sterner, Peterson and Ikeda, questioned the possibility of their representing localized dilatations of one of the collecting ducts emptying into the calyx.

Many of the reported cases presented symptoms, the more common being pain in the region of the involved kidney, colic and hematuria due to renal calculi and symptoms of infection. These cyst-like cavities tend to harbor infection and form calculi due to poor drainage. One case reported by Winsbury-White had hematuria due to hemorrhagic inflammation of the wall without associated calculi. Braasch points out that many pyelogenic cysts do not cause symptoms

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 20, 1952.

and are only discovered during the course of routine pyelography. He also reports that calyceal cysts are usually small.

Operation may be indicated when symptoms are present. The best treatment is a segmental resection of the involved kidney or, as advocated by Prather, excision of the projecting cyst wall and approximation of the walls of the cyst, or dilatation of the communication with the calyx by means of a nephrostomy tube, closing the cyst wall snugly about the tube.

Many of you have undoubtedly encountered this lesion in your practice, probably as an incidental finding during roentgenologic investigation. I believe they are more common than the paucity of the literature would lead one to believe. I wish to present 5 case reports of patients whom I have seen in the past 2 years. None of these have come to operation. Some fall into the classification of incidental findings.



FIG. 1. Case 1. A, retrograde pyelogram showing calyceal diverticulum, right kidney. Small arrow shows communication with upper calyx. B, retrograde pyelogram made with more forcible injection of medium, better visualizing calyceal diverticulum communicating with upper calyx right kidney

#### CASE REPORTS

*Case 1.* An 8 year old girl suffered from at least three attacks of urinary tract infection in the past 5 years. Two of these attacks were severe and were associated with chills and fever. The last attack was unusually severe and the mother volunteered the information that left renal pain and no right kidney pain was a prominent symptom.

When I first saw the child she was asymptomatic and the general examination was essentially negative. A voided urine specimen revealed only the microscopic findings of an occasional pus cell and a few Gram positive diplococci on stain of the sediment. A plain roentgenogram of the kidneys, ureters and bladder revealed normal kidney shadows and no extraneous shadows along the course of the urinary tract. Excretory urograms showed good function in both kidneys, and a grossly normal upper urinary tract.

Cystoscopy proved that the bladder and urethra were normal. Pyelo-uretero-



I first saw the patient in consultation at the King County Tuberculosis Hospital in June 1951. At that time the perineal fistula was rapidly closing without specific therapy. Except for mild urethral pain and urinary frequency, the patient had no complaints. He denied having had any particular pain in either kidney area. A voided urine specimen injected into a guinea pig was reported positive for tubercle bacilli. Cystoscopy on two occasions revealed cystitis of the trigone and vesical neck; moderate contracture and rigidity of the vesical neck; the cavity of a large diverticulum at the base of the prostatic urethra and a bulbomembranous urethral stricture. Study of urine from both kidney pelves was negative for microscopic, routine cultural findings and guinea pig inoculation, on both occasions. A plain roentgenogram of the kidneys, ureters and bladder was negative. Retrograde pyelograms revealed a small calyceal di-

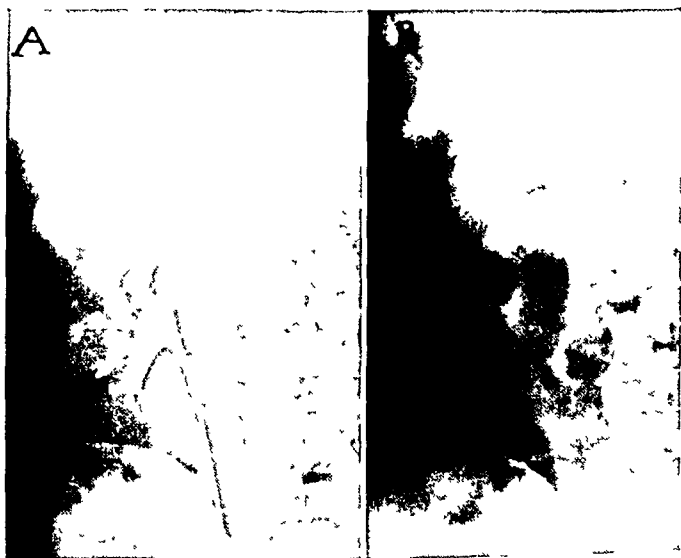


FIG. 4. *A*, case 4. Retrograde pyelogram showing small diverticulum communicating with otherwise normally appearing middle calyx right kidney. *B*, case 5. Excretory urogram visualizing small diverticulum communicating with one of right middle calyces.

verticulum distal to and communicating with the lower, otherwise normal appearing calyx on the right side (fig. 4, *A*). A delayed 10 minute roentgenogram showed no retention of medium in the right kidney.

This case presents a patient with an asymptomatic calyceal diverticulum discovered on routine investigation of the upper urinary tract. It presents an interesting differential diagnosis. I feel reasonably sure that it does represent a calyceal diverticulum in view of the negative laboratory findings. The roentgenographic findings do not suggest tuberculosis. The tubercle bacilli in the voided urine undoubtedly originated from the prostate.

*Case 5.* A 33 year old physician for the first time suffered from urinary frequency, burning on urination, fever and terminal hematuria. Pyuria, erythrocyturia and bacilluria, due to Gram negative bacilli, were found on urinalysis. His acute symptoms rapidly subsided on sulfonamide therapy, but mild pyuria

persisted. A plain roentgenogram of the kidneys, ureters and bladder was normal, and excretory urograms revealed a small calyceal diverticulum coming off the tip of an otherwise normally appearing, middle calyx of the left kidney (fig. 4, B). Cystoscopy and retrograde pyelograms were negative except for the diverticulum demonstrated on excretory pyelograms. Urine specimens from each kidney pelvis were microscopically and bacteriologically negative. The pyuria completely cleared on more prolonged therapy, and to my knowledge, this patient has had no further urologic difficulty for the past 2 years.

This again represents an incidental finding of a small calyceal diverticulum found on routine investigation of a rather persistent urinary tract infection. It could be an etiologic factor in his infection. Observation was advised.

#### DISCUSSION AND CONCLUSIONS

With humbleness, I present these case reports. They are incomplete, as I have no surgical or pathologic findings to give you. I merely wish to call to your attention that the entity of calyceal diverticulum or pyelogenic cyst exists and probably is common enough so that all of us will encounter several examples in our practice. Many of these findings are of no clinical significance except from the standpoint of differential diagnosis. Many produce no symptoms. Some of my cases fall into this category. One cannot determine whether or not infection was the result of these cyst-like cavities. At least the infections did not persist and so far have not recurred. Stones do tend to form in them, as was probably so in two of my cases.

Finally, I have used the terms pyelogenic cysts and calyceal diverticula synonymously. I think they are both good, and I will leave the problem of choosing the more correct to some official committee on urologic nomenclature.

*1503 Medical Dental Bldg., Seattle, Wash.*

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## NEPHROCOLONIC FISTULA: A DUAL CASE STUDY

MILO ELLIK AND JOHN GETZ

*From the Department of Urology of the Los Angeles County Harbor General Hospital and the Medical School of the University of California at Los Angeles*

When a fistula develops between the kidney and the colon it is usually due to perinephritic infection. This somewhat unique syndrome is ordinarily attributed to eroding calculous disease, perinephritis, or tuberculosis. The first of these appears to be the most common, but all represent similar lesions. Modern urological acuity, assisted by better diagnostic aids, has produced most of the relatively few recorded cases within the last 20 years. It is reasonable to assume that there have been many not recognized, or at least not reported. The paucity of such reports, however, seems to indicate an impressive rarity. This fact, that few urologists are privileged to see this uropathy, prompts this presentation of two cases recently seen simultaneously, with an outline of the problems encountered in diagnosis and management.

Nephrocolonic or renocolic fistula was described by Hippocrates. In 1931 Mertz found 29 cases in the literature and added two of his own. His earliest report dated back to 1767. In 1933 Vermooten and McKeown found 2 cases apparently overlooked by Mertz and added one of their own. Wesson reported three in 1938 and a year later Ratliff and Barnes added eight more, including two new ones. Rohrer presented one in 1947, and the latest review by Findlay in 1949 included eight more. The two offered here make a total of 56 reported fistulas of this type.

Previous writers have believed this lesion to be the result of chronic renal inflammation producing a perirenal abscess which ultimately ruptured into the colon. It is generally agreed that such a communication is a sequel to a suppurative renal process, perinephritis, or perinephric abscess. Erosion and rupture into the bowel occur either directly or indirectly through an adjacent suppurative process. This is the most common reno-visceral fistula because of a definite anatomical predisposing factor in that region. Approximately one-third of the anterior surface of the kidney lies in intimate contact with the colon. The peritoneal reflections are such that essentially direct contact between the kidney and the colon exists in a limited area. In practically all cases the fistula has occurred through the cortex from a calyx rather than from the renal pelvis. The primary disease seems to have been universally in the kidney, and erosion from the bowel into the kidney is virtually unknown. None was of neoplastic origin, and Wesson in his discussion aptly reasoned that it would be as difficult for a renal cancer to break through into the colon as for prostatic cancer to penetrate Denonvilliers' fascia into the rectum.

Historical study of patients with nephrocolonic fistulas invariably reveals a recurrent long-standing disturbance of the urinary tract. A classical perinephric abscess, pointing in the flank, may seemingly dissolve, to be followed by the

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 21, 1952.

appearance of blood, pus, and urine in the stools. Pneumaturia, finding of vegetable matter in the urine, or passage of urinary calculi may be observed, and intermittent colic may be a feature. There may be symptoms referable to irritation of the psoas muscle or the diaphragm. Frequency and dysuria may occur with pyuria and hematuria. Debility, with limited local symptoms and urinary changes may add to the diagnostic confusion. The pyelogram can be the first evidence, and it is well to remember that modern antibiotics and chemotherapy may modify the clinical picture beyond ready recognition.

The exact diagnosis usually depends upon visualization of the fistulous tract by pyelographic means. When the fistula drains well the involved kidney cannot be overdistended, since the medium readily escapes into the colon. The cystoscope usually reveals chronic cystitis with infected urine. Excretory urography is unreliable, and the opaque enema has been of value in only 3 cases in the literature. Sometimes the only evidence may be chronic sepsis and unexplained diarrhea.

Treatment often requires initial drainage of the perinephric infection and subsequent removal of the involved kidney. Writers have stressed the importance of ligating the fistulous tract, but it is probably of minor importance, and the bowel, once detached, should close spontaneously. Operative mortality was reported as an impressive 33 per cent prior to the antibiotic era, but surely is much less now.

#### CASE REPORTS

*Case 1.* A 62-year old white woman entered the hospital because of left lumbar pain and swelling, nausea, and vomiting. There was progressive debility of 2 weeks' duration, associated with bladder symptoms. The urine was said to be thick and yellowish. Her past history included 25 years of sporadic urinary symptoms, described as typical bladder irritation, and recurrent painful swellings in the left renal area. She had a persistent heavy feeling in that region and had lost some weight. She had complained of fatigue, anemia, and the abnormal urine for the last 3 or 4 years. Her past medical history was otherwise of no interest, and the family history only in that both parents had died of renal disease and that several of their eleven children had suffered some kind of "kidney trouble."

Examination revealed a chronically ill woman, with a slight fever, a moderately rapid pulse, and no elevation of blood pressure. There was an easily palpable left lumbar mass, quite tender and fluctuant. Urinalysis showed albumin, pus and a few red cells. The culture was negative. The serology was negative, the hemoglobin 9.5 gm. and the white count 17,000. Urea nitrogen was 60. Excretory urography proved unsatisfactory, but the scout film (fig. 1) indicated two small branched calculi in the superior and inferior calyces of the left kidney.

Cystoscopy showed chronic cystitis with hypertrophy of the detrusor muscle. Normal urine and excellent function were found in the right kidney, but a thick purulent drainage was seen from the left ureteral orifice and no indigo carmine appeared from that side. No residual urine was found in either renal pelvis. Retrograde pyelography suggested a reasonably normal upper urinary tract on

the right side, but with some ureteropelvic obstruction, thought to be congenital. The left kidney pelvis accepted 30 cc of skiodan without any pain, and a renocolic fistula was demonstrated (figs. 2 and 3) as the dye was seen to escape into the colon from the upper pole of the kidney.

Surgical drainage of the left perirenal space released more than 200 cc of frank pus, from which *Proteus vulgaris* was grown. There was noticeable subjective improvement, with disappearance of fever and a gain in weight. Attempts to demonstrate the fistula further by injecting skiodan into the sinus in the flank were unsuccessful, as were also skiodan enemas. One month after drainage of the abscess aortography produced a normal vascular pattern in the right kidney, while the left indicated a scanty blood supply with the meagre blood vessel cast more widely separated than usual (fig. 4). The right kidney was then explored and revealed adhesive bands distorting the ureteropelvic juncture. The



FIG. 1. Case 1. Showing small branched calculi in calyces

pyelo-ureterolysis and nephrostomy on that side required another month of convalescence, after which a left nephrectomy was done.

The left kidney was found densely adherent and fixed to the surrounding tissue, but no fistulous tract could be definitely outlined. The pathological report was as follows: "Grossly the kidney is irregularly lobulated and covered by a thick layer of fat. The fat extends into the lobulations along with some fibrous tissue replacing most of the renal parenchyma. The cut surface contains many softened areas which are yellowish-gray in color and occasionally hemorrhagic. A tract, approximately 5 mm. in diameter, smooth and irregular, extends from the tip of a distorted upper calyx through the upper pole of the kidney (fig. 5). Sections of the kidney in the region of this fistula reveal marked distortion and almost complete replacement of renal parenchyma by fibrous tissue containing several large granulomata and many acute and chronic inflammatory cells. The fistulous tract is lined by flattened concentric strands of fibrous tissue

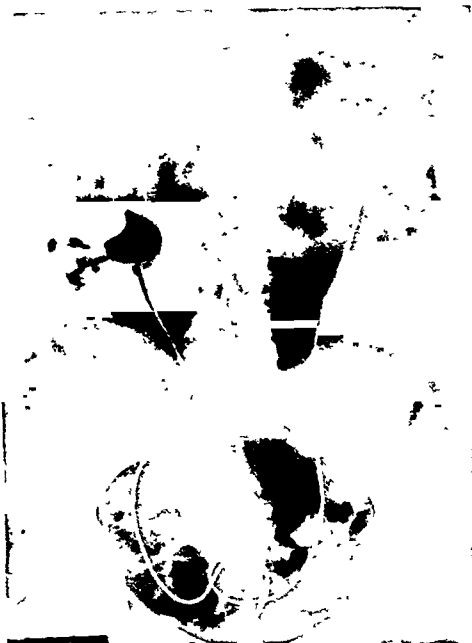


FIG. 2. Case-1. Left pyelogram shows fistulous communication from upper pole of kidney to splenic flexure of colon.

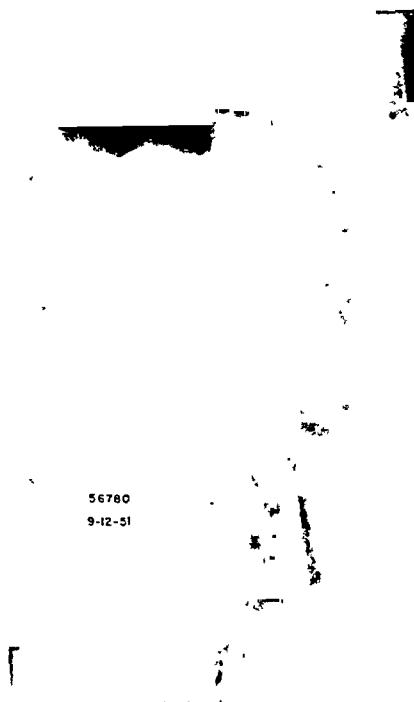


FIG. 3. Case 1. Lateral view of left pyelogram

which contain numerous capillaries, and are heavily infiltrated with lymphocytes. The granulomas have large necrotic centers surrounded by an epithelioid



FIG. 4. Case 1. Aortogram showing normal right renal arterial distribution and distorted left renal arterial pattern.



FIG. 5. Case 1. Surgical specimen showing almost complete replacement of renal parenchyma by fatty and fibrous tissue. Fistulous tract through upper pole is indicated by arrows.

layer and a dense thin fibrous periphery. No tuberculous giant cells are seen and no acid-fast bacilli found. The remaining renal parenchyma is heavily infiltrated with lymphocytes; there is marked intimal and medial thickening of the small and large vessels, and in some instances the lumen is virtually eliminated. There

are scattered clusters of hyalinized glomeruli and dilated tubules containing hyaline casts."

A postoperative fecal fistula developed, but gradually closed within 6 weeks. Antibiotics were administered daily throughout her entire hospitalization. The blood urea nitrogen fluctuated widely between 22 and 77, finally stabilizing at about 27. The urine consistently showed pus, and the culture was proteus. Acid-fast stains were always negative. The patient appeared clinically well when last seen, some 5 months after the original admission.

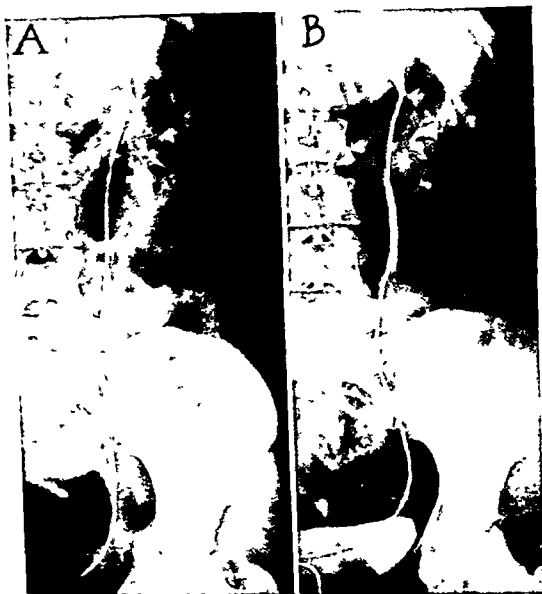


FIG. 6. Case 2. *A*, note evidence of injury and extravasation at lower pole of left kidney. *B*, retrograde left pyelogram during diarrheal phase, showing no evidence of fistula.

*Case 2.* A 28-year old white housewife was injured in a motor accident. Thrown violently under the steering wheel, she lost consciousness momentarily, and then felt a severe pain in the left flank. The first urine passed was very bloody, and subsequent voidings continued so, with some small clots. X-rays revealed no fractures. Her past history included pyelitis during her first pregnancy, but not the second. Retrograde pyelograms made during this complication of pregnancy had shown nothing except the usual dilatation of the pelves and upper ureters. Following the present admission the left flank remained quite painful for 2 days, but finally resolved into a dull ache. Ureteral colic was not marked, fever reaction was minimal, and her general condition remained good. Urological consultation was requested on the eighth day because of persistent hematuria and because excretory urograms indicated an injury to the lower pole of the left kidney. Retrograde pyelography corroborated this (fig. 6, *A*), but no real mass ever developed in that area. Despite some difference of opinion, surgery was deferred in favor of so-called conservatism. The patient remained under constant hospital surveillance. Gross hematuria continued briskly for 2 weeks,



the urine then becoming clear but with microscopic blood. The clinical picture seemed to indicate a spontaneous healing. On the twenty-third day after the accident a peculiar type of diarrhea occurred, accompanied by fever rising to 104°F, rapid pulse, malaise, and marked apprehension. The flank findings were unchanged. There seemed to be no evidence of a food or bacterial sensitivity, laboratory tests of the stool were not helpful, and standard therapy failed to control the watery evacuations which at times were too numerous to tabulate. Since we believed that there must be some relation between the renal injury and the diarrhea, test doses of methylene blue by mouth and indigo carmine intravenously were given. Both dyes appeared in copious amounts in the bowel movements. It appeared obvious, therefore, that urine was reaching the intestine, and that the diarrhea was essentially urinary drainage. Retrograde pyelography (fig. 6, *B*) and enemas failed to outline the fistulous tract, and the urine remained grossly normal with the number of erythrocytes decreasing. This inspired the belief that the renal pelvis did not connect directly with the bowel, but that the fistula led from the ruptured cortex through a perirenal hematoma into the colon. The diagnosis of nephrocolonic fistula was made, even though the communication could not be radiologically shown. A conservative course was still followed and antibiotics seemed eventually to control the situation, the diarrhea ceasing completely after 12 days. The patient was discharged after a total hospitalization of 6 weeks, and was apparently entirely well.

During the next six months, at almost monthly intervals, there occurred similar attacks of diarrhea, fever, malaise, and left flank pain, at which times the blue dyes were given her and appeared in every watery stool. As the diarrhea came under control with antibiotics the dye appeared only in the voided urine. Further judicious attempts at radiological demonstration of a fistulous tract failed. The left pyelogram was essentially normal, the tenderness was negligible, no palpable mass ever appeared, and the patient's general condition remained quite good. There was a mutual hope that every attack would be the last. Finally an unusually severe session of diarrhea, fever, and pain prompted surgical intervention, and six and one-half months after the original injury the kidney was removed.

No fistulous tract was actually demonstrated at surgery, but adhesions about the lower pole of the kidney were intimately associated with the adjacent colon. No abscess cavity was actually seen either, but it was quite obvious that in the injury the lower pole of the kidney had been torn completely across. Spontaneous healing of this defect had been exceptionally good, and the upper uninjured segment of the kidney appeared normal and without adhesions. The pathologist reported that the kidney contained a depressed area demarcating the lower pole, measuring 50 by 35 by 30 mm. The depressed line of rupture was adherent to the fatty tissue. Microscopically an area of fibrosis marked the exceptionally well-healed fracture line. There were focal areas of subcapsular fibrosis and lymphocytic infiltration adjacent to the scarred area. No definite fistula was demonstrated.

Her postoperative progress was serene, healing occurred promptly, and no fecal drainage was seen. She was dismissed from the hospital on the tenth day, ambulatory and afebrile. Now, a few months later, she has shown no return of symptoms. The blue dyes have never appeared in the stools, in spite of the fact that an occasional diarrhea from food sensitization has offered us an opportunity to make the test. Her general good health and physical condition continue.

#### COMMENT

We believe that one of these cases is unique in that the diagnosis of fistula following the ruptured kidney hinged upon the excretion of dyes ingested or injected intravenously, when the usual radiological proof could not be obtained. Studies of methylene blue and indigo carmine indicate some slight elimination by organs other than the kidneys, but this is so minute that their only appreciable excretion is through the urinary tract, and their appearance in the bowel proves fistula. Rohrer suggests that only one other case in the literature gave a history of trauma, though his own patient had an old traumatic background. Possibly in our case the urinary drainage came from the detached lower pole rather than from the pelvis which showed no communication. If this lower pole had a blood supply and excreted urine it may have used the colon as its drainage system.

Our other case was of the stone eroding form, and appears to be of the classical type with a progress similar to many others reported. The only novelty in this instance was the diagnostic use of aortography, which we thought was very helpful in prognosis.

Nephrectomy still appears to be necessary for cure, though every modern conservative method was tried in the case of ruptured kidney. Antibiotics served only to produce a more bizarre clinical picture, although they may have softened the subjective blow. This presentation should stimulate an awareness of this syndrome as an aftermath of trauma to the kidney, and any unusual diarrhea in such patients should be investigated. The fistulous tract itself apparently presents no great problem in treatment, and may not require ligation or even identification at the time of surgery.

#### SUMMARY

Two cases of recent nephrocolonic fistulas are presented, one of the classical stone eroding type, the other a sequel of a rupture of the kidney.

In the absence of the usual radiological proof of communications of this type, the existence of a fistulous tract may be verified by the administration of methylene blue or indigo carmine.

The use of aortography was considered of definite value in the management and prognosis in one case, and may therefore be recommended.

These fistulous tracts need not be actually demonstrated at surgery, their surgical closure is optional, and the released colon can be expected to close spontaneously.

Antibiotics serve only for the temporary control of infection, may produce a bizarre clinical picture, and leave nephrectomy as still the only adequate cure.

*117 E. Eighth St., Long Beach 13, Calif. (M. E.)*

*Los Angeles County Harbor General Hospital, Torrance, Calif. (J. G.)*

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## FACILITATION OF PASSAGE AND EXTRACTION OF URETERAL CALCULI

EARL F. NATION

The Johnson stone extractor remains for us the most reliable and efficient instrument for the extraction of calculi from the lower ureter. This is largely the result of our criteria for the manipulation of calculi.

Any stone of less than 1 cm. in diameter we consider to have a chance to pass spontaneously. Ureteral catheterization and stone manipulation are avoided: 1) as long as occasional excretory pyelograms do not disclose an undue degree of hydronephrosis and impaired renal excretion; 2) in the absence of fever or intractable pain, or pain requiring an inordinate amount of sedation over too long a period of time.

After the initial pain and spasm are relieved, the patient is observed and followed with scout films at weekly intervals and excretory pyelograms every 2 to 4 weeks as indicated. Such patients are occasionally followed in this manner for a period of several months before a stone passes. They go about their affairs and suffer no inconvenience. The majority of ureteral stones which we see will pass in this manner without any manipulation and without demonstrable renal damage. We have surgically removed calculi of 3 cm. or more in diameter from the lower ureter of 3 patients in whom they had been present for several years without pyelographic change or damage to renal function.

Serious complications of ureteral stone manipulation are not uncommon. Such disasters should not be courted needlessly. When obstruction, fever or intractable pain occur or a calculus is not progressing after a reasonable period of observation, an effort must be made to extract it if it is of suitable size and in proper position. Occasional accidents or complications of the maneuver must be accepted as a calculated risk. When the kidney is completely obstructed or there is doubt about being able to get beyond the calculus with the extracting instrument, complications may be minimized by the insertion of an ureteral catheter for two or more days preceding other manipulation. If the stone is in the upper half of the ureter, an Ellik extractor may be inserted and left in place.

The most difficult, uncertain and hazardous part of any stone extraction is the introduction of the extractor beyond the calculus. Once this is accomplished the chances of removing the stone are immeasurably increased.

It has been our experience in manipulating calculi in the lower ureter to pass the calculus with the filiform guide and basket the first time, and upon withdrawing the basket without engaging the stone to be unable to again pass by the obstructing calculus. To overcome this difficulty it occurred to us to try a longer filiform guide than the 6-8 cm. one recommended by Johnson.<sup>1</sup> For this purpose we have used the regular 15 or 33 cm., 2 or 3F filiforms which are manufactured to fit the Phillips catheters and Le Fort sounds. These may be obtained with the same thread as that of the Johnson stone extractor (fig. 1).

The 33 cm. filiform guide is most useful, being readily introduced and manipu-

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 21, 1952.

<sup>1</sup> Johnson, Franklin P., *J. Urol.*, 37: 84-89, 1937.

lated through the Braasch cystoscope and the McCarthy panendoscope. When the guide has been inserted into the ureter, the Johnson stone basket is attached to it and passed through the cystoscope and up the ureter. The 15 cm. filiform guide, like the shorter guide, is attached to the stone extractor before its introduction through the cystoscope. The basket with the 15 or 33 cm. guide may

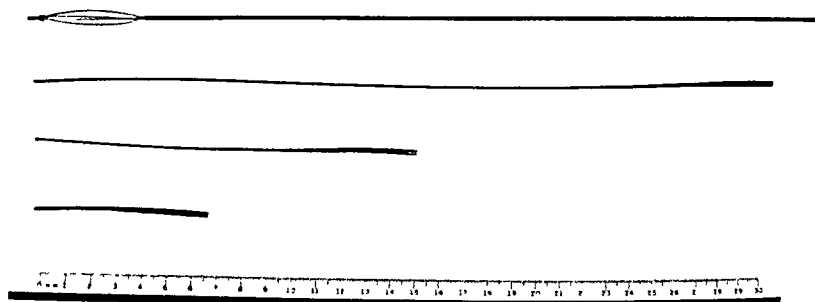


FIG. 1. Standard filiform guide, 15 cm. filiform, 33 cm. 2F filiform guide and Johnson stone extractor.



FIG. 2. *A*, showing calculus in lower left ureter. *B*, excretory urogram showing slight dilatation above calculus.

then be introduced beyond the calculus and withdrawn from the ureteral meatus under cystoscopic vision as many times as necessary without the danger of again being unable to pass beyond the calculus because the long filiform guide is not pulled below the obstructing stone. These flexible guides of small diameter seem to be especially efficient in passing obstructing calculi. In addition, they obviate the principal danger of perforating the ureter at the site of the impacted stone by the exertion of too great a force on the stiff stone extractor and short filiform

guide. No harm follows the introduction of this very flexible instrument into the renal pelvis if necessary. Spiral and Coudé tipped guides may be tried in difficult cases. The Braasch cystoscope is particularly efficient for the described stone manipulations, as it is for overcoming most ureteral obstructions.

#### CASE REPORT

The following case, the first in which the long ureteral filiform guide was used, illustrates its effectiveness:

Mr. J. M., a 55 year old laborer, came to the office April 13, 1949, with a history of left renal colic of 1 day's duration. He had had a similar pain 2 months previously and had passed a calculus from the left kidney 4 years ago. A scout film showed a 4 by 8 mm. calcific density in the region of the lower left ureter. Excretory urograms disclosed slight dilation of the upper urinary tract on the left (fig. 2).

During the course of 6 weeks' observation, the stone did not progress. On May 25, 1949, efforts were made to introduce the Johnson stone extractor beyond the obstruction, using the conventional short filiform guide, without success.

On June 17, 1949, no further progress having occurred, the Johnson stone extractor again was introduced, using the short filiform, this time under spinal anesthesia. It was passed beyond the calculus and a small fragment was broken off. Following this nothing would go beyond the obstruction.

On August 26, 1949, and again on November 21, 1949, the calculus was manipulated with like results. The patient was checked regularly by excretory urography to insure the kidney was draining adequately.

Finally, on November 23, 1949, using the long filiform guide for the first time, the Johnson stone extractor was introduced beyond the calculus repeatedly until it was engaged. It was then drawn down to the ureteral meatus. The Braasch cystoscope was removed and a McCarthy pan-endoscope was introduced beside the shaft of the stone extractor. An ureteral meatotomy was done with the Collings knife and the stone easily withdrawn in the basket. This latter maneuver has been used successfully on many occasions for extracting large stones through the ureteral meatus without excessive tension and trauma. Ureteral meatotomy in such cases is sometimes avoided by placing gentle tension on the Johnson stone extractor for 24 to 48 hours, leaving a small Foley catheter in the bladder for drainage.

Since this experience, one of the longer filiform guides has routinely been used and is successful in a great majority of cases.

#### SUMMARY

Conservative principles of ureteral stone management are outlined and advocated.

The use of a long filiform guide for the Johnson stone extractor in certain instances of lower ureteral calculus is proposed. This facilitates the repeated safe introduction of the extractor beyond the calculus when this is necessary. An illustrative case is presented.

*112 N. Madison Arc., Pasadena 1, Calif.*

## A NEW URETEROPLASTY: ADVANCEMENT OF THE URETER BY A VESICO-URETERAL PEDICLE GRAFT

ROBERT B. HIGGINS

*From the Department of Urology, Massachusetts General Hospital, Boston, Mass.*

Conservative management of the long ureteral stricture is unsatisfactory, for it frequently results in the loss of one kidney or at least in the use of a nephrostomy. The purpose of this paper is to present an operation for bridging irreparable ureteral defects caused by strictures or injuries at any level. The circulation of the ureter and its relative autonomy are discussed insofar as they are germane to the procedure. Other attempts to correct the severe ureteral defect have been reviewed.

No satisfactory method exists for establishing ureteral continuity where the ureteral wall has been essentially lost over a long segment. The simple primary stricture is not the problem, for there are many established methods for correcting it. The simple, long ureteral stenosis should not be included, for the Davis intubation procedure is simple and quite effective. Under consideration, is the occasional troublesome case where a large segment of ureter has been shot away; where a long secondary stricture exists with a tortuous channel, much peri-ureteral fibrosis and infection; where much operating has rendered local reconstruction impossible; in short, where ureterostomy, nephrostomy or nephrectomy have been performed in the past. But these compromise measures are unsatisfactory. In general, because they sacrifice renal function or the reservoir function of the bladder. Therefore, a method for bridging these defects is needed.

The following case report indicates the difficulties of the problem and the operative solution devised.

### CASE REPORT

A 33 year old, single, operating-room supervisor first began to experience trouble associated with a horseshoe kidney 12 years ago. Her subsequent clinical course involved persistent, recurrent renal infection, increasing ureteropelvic obstruction and the failure of repeated surgical attempts to alleviate the ureteral obstruction and the renal infection. The details are too numerous and involved to be included in this paper. After twenty-five hospitalizations at various institutions, the right kidney had been removed, and four operative attempts to correct the left ureteral obstruction had failed.

The nephrostomy catheter was indispensable and yet unmanageable, in spite of faithful care. Her symptoms of renal obstruction and infection demanded attention. Again, she was admitted to the hospital. Physical examination at this time revealed obesity, apical abscesses of many teeth, normal heart and lungs; blood pressure 120/80, multiple healed incisions of both flanks, left lower quadrant tenderness and left nephrostomy, a normal cervix and uterus with no adnexal mass by pelvic examination and rectal examination, and no other apparent

anomalies. Urinalysis: 50 to 80 white blood cells per high power field, abundant *B. proteus* and *B. coli*, and a specific gravity of 1.020. The blood hemoglobin was 14.2 gm. and the white blood cell count was 12,400. The blood nonprotein nitrogen, total protein, prothrombin time,  $\text{CO}_2$  and chloride were normal. Renal function had deteriorated as evidenced by a 53 per cent urea clearance and a 30 per cent phenolsulfonphthalein excretion. Direct pyelogram revealed a tortuous, narrowed ureteral channel just below the renal pelvis for about 6 cm. and ureteral catheterization was impossible from above or below.

Thus, in March 1951, after thirty hospital admissions and six operations, a young, intelligent nurse was again in the hospital with these problems: 1) a single kidney, with markedly diminished function and with severe hydronephrosis, 2) persistent urinary tract infection caused by *B. coli* and *B. proteus*, 3) extensive tortuosity and stenosis of the upper ureter, 4) massive peri-ureteral fibrosis and infected tissue caused by previous operations and 5) a malfunctioning nephrostomy.

We felt that the patient's age and position in life and her apparently untenable situation justified another major reconstructive effort. The existing procedures were carefully considered and eliminated for fundamental reasons.

An operation was planned, involving the advancement of the left ureter in the tip of the bladder pedicle graft, and one ureteral anastomosis. The procedure is best understood by referring to the accompanying drawings (fig. 1). First of all, the operation required a good exposure, which was gained through a thoracolumbar incision, made over the eleventh rib diagonally downward to the symphysis pubis. The diaphragm was split for a short distance, and the pleura was pushed up out of the field. This made possible a painstaking dissection of the urinary tract entombed superiorly in thick scar and the difficult liberation of the bowel also incarcerated.

Following this, the lime-sized ball of scar surrounding the upper ureter was excised, leaving a 7 cm. gap between the renal pelvis and the end of the ureter. With its intact adventitial vessels, the ureter was mobilized inferiorly; the left ovary was retracted medially; and the branches of the hypogastric artery and vein were divided as far from the bladder as possible in order to preserve the small, anastomosing arborizations between the ureter and the bladder wall. The peritoneum was dissected away from the superior and left lateral part of its vesical attachment. At this point, the whole left side of the bladder, including the left half of the bladder floor, was free from surrounding structures. Care was taken not to disturb the right bladder base or pedicle.

The incision of the bladder was carefully mapped out so as to produce a long curved, wedge-shaped pedicle graft (fig. 1, I, II). The base of the graft was at the right posterosuperior aspect of the bladder. The apex of the wedge was cut from the under side of the bladder, including the left ureterovesical orifice. Thus two converging lines of incision were begun at the right bladder dome and extended diagonally, from right to left, downward over the anterior surface of the bladder, to an area lateral to the left side of the urethra. From here, one incision divided the trigone; and the other passed lateral to the left ureteral orifice, and joined



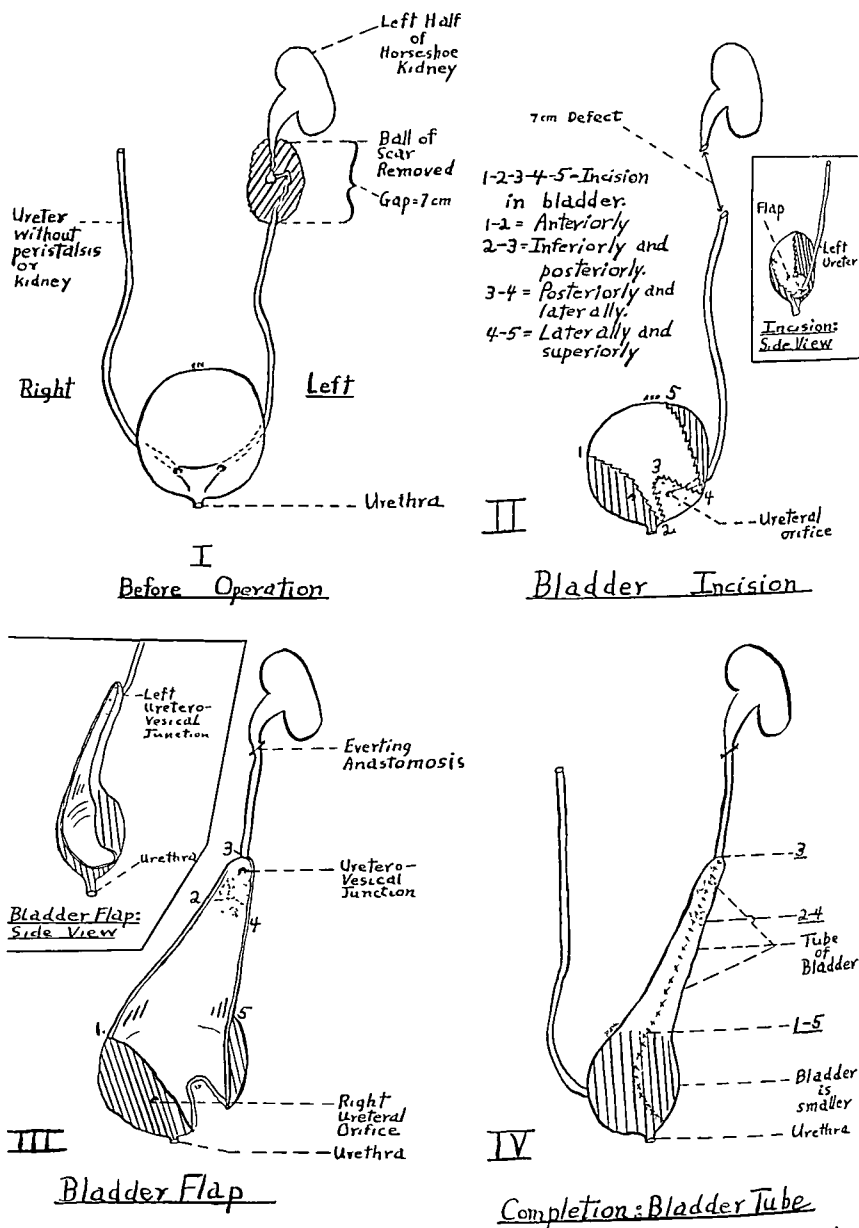


FIG. 1. *I*, Before operation; solitary half of horseshoe kidney, peri-ureteral fibrosis, and ureteral tortuosity. *II*, bladder incision with front and side view; 1-2-3-4-5 traces incision; 1-2 anteriorly; 2-3, inferiorly and posteriorly; 3-4, posteriorly and laterally; 4-5, laterally and superiorly. Stippling indicates tip of bladder flap. *III*, Bladder flap with front and side view showing preserved ureterovesical junction and everted anastomosis. *IV*, Completion: Bladder tube; bladder is smaller; ureteral gap is bridged.

the first at a point posterior to the ureteral orifice. Packing the bladder with gauze helped to preserve its symmetry, while the flap was being cut.

When this curved wedge of bladder wall was unrolled upward, the uretero-

vesical orifice was elevated for a distance of 15 cm. (fig. 1, *III*, *IV*). This elevation, of course, allowed a 15 cm. advancement of the ureter itself upward toward the renal pelvis. This was more than enough to bridge the gap, and so, the excess was cut away.

The bladder flap was then rolled into a tube with fine running catgut suture. The bladder proper was reconstructed. The ureter and the pelvis were anastomosed with three fine, continuous catgut sutures, triangulating and everting the oblique anastomosis after the fashion of vascular surgery. No splint was used.

The result was a smaller bladder with a horn constructed upon it. The ureter seemed to insert into this horn in a normal fashion. A large vein ran in the wall of the ureter from the anastomosis to the bladder wall.



FIG 2 *A*, preoperative retrograde pyelogram. Arrow indicates ureteral defect. Nephrostomy catheter in place *B*, preoperative pyelogram via nephrostomy catheter shows severe hydronephrosis.

In the latter part of this long difficult procedure, intra-arterial transfusions were used to combat the severe hypotension. Blood loss, however, was small. The wound was closed with dispatch and numerous wire stay sutures. The nephrostomy catheter was readjusted.

The postoperative course showed steady improvement. Immediately, the flow of urine manifested return of renal function. The first week, however, was marked by severe, acute pyelonephritis, which was met adequately by the administration of penicillin and streptomycin and supportive measures. Blood chemistries remained normal. Urine drained from the bladder catheter, as well as from the nephrostomy in large amounts.

Three weeks after operation, cystoscopic instrumentation of the nephrostomy channel permitted passage of a No. 10 catheter into the bladder, easily; an x-ray revealed an intact, patent anastomosis. Irrigation into the kidney, down the

ureter, and out the bladder catheter, was visible proof of the result. Later, by making the cystoscope navigate the bladder tube, we were able to pass a catheter up the left ureter to the renal pelvis. Therefore, 51 days after operation, the nephrostomy catheter was removed; the sinus promptly closed.

The result of the operation is satisfactory. Since discharge, the patient has consistently felt well. Renal ability to excrete nonprotein nitrogen and to concentrate the urine is unchanged, according to test. The preoperative excretion of phenolsulfonphthalein was 32 per cent in 2 hours; postoperatively the phenol-sulfonphthalein excretion was as good or better in each of the four specimens

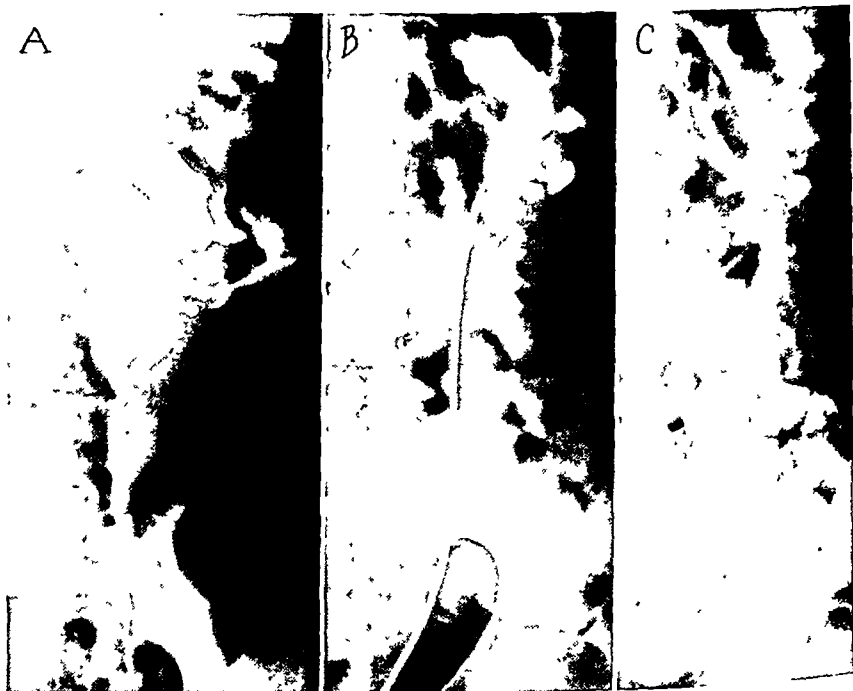


FIG. 3. A, 1 month after operation, pyelogram through nephrostomy catheter; arrow indicates anastomosis. Drainage down ureter is rapid. Dye on patient's back is visible. Apparent obstruction is not real as is seen in B and C. B, passage of No. 10 polyethylene catheter 2 months after operation and retrograde pyelogram. C, film made 5 minutes after B shows prompt renal drainage.

collected with a two-hour total of 35 per cent. Although the *B. proteus* seemed to have been eliminated with the great improvement in the patient's nutrition, all chemotherapy has been ineffective in sterilizing the urine. Gross anatomy of the kidney remains the same, as is seen in the accompanying x-rays (figs. 2, 3 and 4). The lumen of the anastomosis had continued to allow easy passage of an 8-10F catheter, 14 months following operation. Pyelograms demonstrate adequate drainage. At cystoscopy, indigo carmine has been seen to come from the ureter in spurts as if by ureteral peristalsis. The postoperative neurogenic bladder was handled by an indwelling catheter and intermittent emptying for 5 months. One month after catheter removal, she demonstrated a 325 cc vesical capacity

with 30 cc residuum. Cystometrograms fail to show clear signs of normal detrusor activity; but it seems that the artificial vesical diverticulum accounts for this. Practically, her voiding is no problem. A cystogram, made while she voided against resistance, failed to show significant ureteral reflux.

For the first time in 13 years, the patient constantly feels well; at the time of this writing, 17 months since her operation.



FIG. 4. Cystogram, 2 months after operation, shows no reflux when bladder is filled to limits of patient's tolerance. Arrow indicates bladder tube manufactured.

#### LITERATURE

In the development of this procedure, the literature was carefully reviewed to discover what techniques others had used in reconstruction of severe ureteral defects and what results others had observed with this type of reconstruction. No instance was found where the above operation was performed, previously.

Many kinds of free grafts fail to provide satisfactory reconstruction. The use of free fascial or peritoneal grafts or free bladder grafts has been shown to fail (Lord et al., 1943); but, over vitallium tubes, fascial grafts in dogs' ureters resulted in an epithelialized canal without stricture (Lord et al., 1943). However, peristalsis was not provided for, since the muscular elements were lacking. The same objection exists for the use of free vein grafts or split-thickness skin grafts, or free grafts of bladder mucosa. Free ureteral grafts are too thick to survive without some blood supply and could be expected to become fibrosed as in the case of ureteral grafts of the common duct (Sedgewick, 1951). The intubated ureteroplasty causes reappearance of an intact muscle layer in dogs in the area of the stenosis when used in lesions up to 10 cm. long (Davis, 1947 and 1948). But, in humans, this regeneration has not been shown to occur where there is a

total loss of the ureteral wall over this distance. The muscle cells would have to grow from the healthy ends through granulation tissue and scar. The very conditions of the problem under discussion, i.e. infection and fibrosis, discourage regrowth of tissue. The case presented demonstrates failure of this method on two occasions under these conditions.

The pedicle graft offers the best opportunity for cure. Skin tubes swung into place have connected the ureter and bladder successfully, but fail to provide a muscular wall (Bettman, 1940). In 1940, Nissen successfully interposed a segment of small bowel between ureter and bladder of man in 1 case. However, this ingenious procedure involves three anastomoses and does not avoid ureteral reflux. Along these lines men have devised, in animals and men, a bladder flap into which the ureter was implanted. Boari, in 1894, first described the use of a bladder flap in dogs. He reported the use of the carotid artery of dogs for ureteral reconstructions in the same article. Glass tubes were also used. He reviewed all of his work in an excellent volume on the ureter in 1900, where he described the use of a horn of uterus and a segment of small bowel in dogs. His most successful contribution in ureteral reconstruction was in the use of bladder flaps with re-implantation of the ureter. He has one 4-year follow-up of the latter procedure in a hunting dog which hunted as well as ever after operation. Demel, in 1924, incised the bladder of dogs in such a way as to produce a bicornuate bladder implanting the ureter into the superior horn. Baidin, in 1930, first reported successful use of this method in a man with a four-year follow-up; Boeminghaus in 1931 reported use of this method with some success. In 1932, Spies, Johnson and Wilson reported experimental work with bladder flaps in dogs. Rhode, in 1937, also reported this method. In 1940, Gomoiu used a bladder flap with ureteral re-implantation for two-stage repair of a large vesicovaginal fistula. In America, Ockerblad reported, in 1947, success with implantation of the ureter into a bladder flap in humans. In 1948, in 11 calves, Barnes and Farley studied the same procedure. In summary, most of the authors were plagued with anastomotic strictures or ureteral regurgitation. The follow-ups were too short and the numbers too few to be significant. It seems most important to preserve the ureterovesical junction.

#### PLANNING

The latter observation was the basis for the devised procedure. In cadavers flaps were easily cut from the bladder which provided 15 cm. of extra ureteral length and preserved the ureterovesical junction. The position of the bladder tube was easily constructed so as to be lateral to a uterus enlarging with an embryo. Several problems were obvious.

*Ureteral circulation.* First, it was necessary to sever unilaterally all the important vascular supply to the bladder and to sever all vascular supply to the affected ureter, expecting that which was derived from the base of the bladder *opposite* to the damaged ureter. We wondered if the anastomotic circulation of the ureter was efficient; we wondered if the flow of blood from the *right* bladder base up into the bladder flap on the *left* side and into the ureter concerned would

nourish a ureteral anastomosis sufficiently; above all, we wondered if the venous drainage would be adequate.

The necessary severance of ureteral blood supply, at first, seemed hazardous. Yet, evidence from many sources supported the belief that, if one point of major vascular supply was intact, the anastomotic circulation of the ureter would distribute the blood in sufficient fashion. Two German publications at the turn of the century described extensively the ureteral circulation from work in dissection and microscopic examination (Disse, 1903; Protopopow, 1897). The main arterial and venous trunks enter at several points. From the main renal vessels or their radicles, an important vessel enters the ureter. There is usually a branch of supply from the spermatic or ovarian vessels and from the lower abdominal aorta and inferior vena cava. There is quite constantly a branch from the common iliac vessels or external iliac vessels or from the hypogastric vessels at their source. Inferiorly, the ureter is supplied in varying ways from the various branches of the hypogastric arborization and from the vessels of the bladder itself. According to Michaels, the renal and middle vesical arteries are the most constant and important sources of blood. Disse and Protopopow also state that all these vessels send branches upward and downward, freely anastomosing, not only in grossly visible trunks in the adventitia of the ureter, but, also in microscopic networks in the submuscular layer and in the subepithelial layer. Thus, there are three sets of vascular channels along the entire course of the ureter. Severance of many vessels failed to change peristalsis as long as there remained one or two major vessels of supply. Sampson further supported this point by injections of the ureteral vessels of cadavers with a 15 per cent ultramarine blue gelatin solution. He could inject any vessel with the others severed and produce visible dye in all parts of the ureter. It even showed up on the peri-ureteral submucosal vessels of the bladder.

We took additional heart from numerous observations on cadavers and at operation where the adventitial longitudinal circulation was visible. Also, experience with skin ureterostomies, where the blood vessels of supply are severed often up to the kidney itself without ill effect, seemed to lend corroboration. Finally, the excellent anastomotic circulation of the bladder itself was heartening; for the former was to serve the base of the flap.

*Ureteral peristalsis.* The second problem was preservation of the ureteral peristalsis when the ureter was almost completely rendered autonomous by denervation. From new and old works, the effect of extensive severance of nerve branches to the ureter was shown to have less effect than the loss of blood vessels (Protopopow, 1897; Satani, 1919; Lapidès, 1948). Peristalsis is not affected. Direct observation of ureteral peristalsis at the skin in skin ureterostomies would support this.

*Neurogenic bladder.* Thirdly, we fully expected to produce, temporarily an autonomic neurogenic bladder. Severing the fibers of the parasympathetic outflow of the anterior roots of  $S_2$  and  $S_3$  (and sometimes  $S_1$  and  $S_4$ ) bilaterally produces an autonomic bladder permanently. But, if only side is cut, it is stated that the intact side provides for normal bladder function in a matter of months (Lang-

worthy et al., 1940; McLellan, 1933). Yet, preservation of the ureterovesical junction seems to justify the consequent temporary denervation of the bladder. For many have demonstrated that ureteral reflux occurs seldom through a natural ureterovesical junction, but often through a manufactured one (Graves et al., 1923, 1925). Sampson pointed out that ureteral reflux was often important in renal infection. Work with neurogenic bladders certainly supports his statements.

The absence of reflux in the case reported bears out the above contentions.

With broader significance, the survival of the ureteral anastomosis in this case demonstrated the excellent intrinsic circulation of the ureter, and indicates one solution of a difficult, specific, surgical problem.

#### SUMMARY

An original operation is presented whereby a vesical horn was constructed, preserving the ureterovesical junction and allowing advancement of the ureter upward for a distance of 15 cm. The literature contains no description of such a procedure.

The patient was a young woman who started life with a horseshoe kidney. After six operations, she possessed a nephrostomy and a severe stricture of the ureter draining a solitary kidney. Operative reconstruction easily bridged the 7 cm. gap with excess ureteral length. The postoperative result was good.

The literature and planning of the procedure are discussed, including the ureteral anatomy and physiology.

#### CONCLUSIONS

The irreparable, ureteral defect can be bridged from 12 to 15 cm. by this method.

The longitudinal, anastomotic circulation of the ureter compensated for the severance of the main arterial supply, in this case.

44 Cypress St., Newton Center, Mass.

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worthy et al., 1940; McLellan, 1933). Yet, preservation of the ureterovesical junction seems to justify the consequent temporary denervation of the bladder. For many have demonstrated that ureteral reflux occurs seldom through a natural ureterovesical junction, but often through a manufactured one (Graves et al., 1923, 1925). Sampson pointed out that ureteral reflux was often important in renal infection. Work with neurogenic bladders certainly supports his statements.

The absence of reflux in the case reported bears out the above contentions.

With broader significance, the survival of the ureteral anastomosis in this case demonstrated the excellent intrinsic circulation of the ureter, and indicates one solution of a difficult, specific, surgical problem.

#### SUMMARY

An original operation is presented whereby a vesical horn was constructed, preserving the ureterovesical junction and allowing advancement of the ureter upward for a distance of 15 cm. The literature contains no description of such a procedure.

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## TRANSPERITONEAL APPROACH TO LESIONS OF THE LOWER URETER

BERNARD R. SEARS AND JOHN W. SCHULTE

*From the U. S. Veterans' Administration Hospital, San Francisco, and the Department of Surgery (Urology), University of California Medical School*

It has long been established that the extraperitoneal route is generally adequate for surgery of the lower ureter, and no effort is made here to suggest its abandonment. In secondary operations, however, extraperitoneal dissection is often beset by difficulties and hazards which may be lessened by a transperitoneal approach. Among these are dense fixation of the peritoneum to the pelvis, difficulty in locating the ureter and its lesion (usually a calculus), and the possibility of injury to the pelvic viscera and the great vessels. We propose to call attention to the transperitoneal exposure of the lower ureter as the method of choice in selected cases, to mention some maneuvers that may at times promote the success of the procedure, and to emphasize the relatively slight risk of peritonitis, adhesions, and subsequent intestinal obstruction.

Only a few references to this procedure are in the literature, our survey showing only 26 cases. Thomson-Walker<sup>1</sup> gives a mortality of 5.5 per cent for transperitoneal ureterolithotomy, but does not indicate his personal experience nor the source of his statistics. We must exclude Deaver's<sup>2</sup> 12 cases of ureterotomy combined with appendectomy because after closing the peritoneum following appendectomy he approached the ureter extraperitoneally. They are noticed, however, because they are somewhat similar to present subject. Kneise<sup>3, 5</sup> in 1941 described the largest series of 18 personal cases. Three were reported by Dick<sup>6</sup> two by Sweetnam,<sup>7</sup> and one each by Eisendrath,<sup>8</sup> Tatayama,<sup>9</sup> and Dobritz.<sup>10</sup> All but one were operated upon for calculi, and the only death occurred in one of Kneise's patients who entered the hospital in anuria and remained so after the removal of the stone.

Of principal interest are the reports by Kneise and by Dick. Kneise operated on

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 21, 1952.

<sup>1</sup> Thomson-Walker, Sir John W.: *Surgical Diseases and Injuries of the Genito-urinary Organs*. London: Cassell, 1936, 2nd ed., p. 308.

<sup>2</sup> Deaver, J. B. and Burden, V. G.: *The surgical management of stone in the ureter*. Ann. Surg., **91**: 85, 1930.

<sup>3</sup> Kneise, O.: Eine neue Transperitoneale Operation juxtavesikaler bei der Frau. Zentralbl. f. Gynak., **59**: 483, 1935.

<sup>4</sup> Kneise, O.: Transperitoneal ureterolithotomy with special reference to the Kneise method. Urol. & Cutan. Rev., **44**: 99, 1940.

<sup>5</sup> Kneise, O.: Weiteres zur Frage der Transperitonealen Ureterolithotomie. Ztschr. f. Urol., **35**: 100, 1941.

<sup>6</sup> Dick, V.: Secondary surgical procedures on the low ureter. S. Clin. North Amer., **30**: 933, 1950.

<sup>7</sup> Sweetnam, H. W.: Transperitoneal removal of stone impacted in pelvic portion of the ureter. M. J. Australia, **2**: 819, 1928.

<sup>8</sup> Eisendrath, D. N.: A simplified technique for removal of calculi in the pelvic portion of the ureter. Surg. Gynec. & Obst., **48**: 245, 1929.

<sup>9</sup> Tatayama, R.: Über einen Fall von Intraperitonealer Exstipation eines Uretersteines. Zentralbl. f. Gynak., **49**: 1134, 1925.

<sup>10</sup> Dobritz, O.: Zur Transperitonealen Ureterolithotomie. Ztschr. f. Urol., **36**: 404, 1942.

16 women and two men. Three of the patients had infection in the urine, and the author describes a technique of placing drains near the ureterotomy, but does not make it clear that he did so. Sweetnam and Tatayema state that they did not use drains. Kneise recommends the operation for "juxtavesical stones in obese patients," but notwithstanding his success with three infected cases believes that urinary infection is generally a contra-indication to this procedure.

Dick was the first to suggest the transperitoneal route for secondary operations on the ureter. His 3 patients all had mixed urinary infection, recognized before the operation. Two had calculi and the third a solitary kidney with a strictured ureter that had previously been operated upon. In his first case he first attempted an extraperitoneal dissection, but "dense fibrosis and considerable bleeding made this impracticable so the peritoneum was opened widely (it had already been entered in several places), the bowel packed away, and the presumed area of the ureter visualized." In order to identify the ureter Dick opened the bladder and passed a silver probe up the ureter. When the definitive part of the operation was completed, he says "... what had started as a most difficult piece of work had been easily accomplished." Extraperitoneal drainage of both ureter and bladder was established. In his second and third cases he followed the same plan, except that celiotomy was performed at the outset.

#### CASE REPORT

A 56-year-old man (SF VAH, REG. No. 47214) entered the hospital with a history of 24 hours intermittent cramping pain in the right costovertebral angle and the lower right quadrant. A 3-glass test of the urine showed a few red cells in each specimen. He previously had had stones removed surgically from the lower portion of each ureter.

Excretory urography and cystoscopy were done the first day. The urograms showed no dye excretion by the right kidney, but there was a calcific density overlying the right sacroiliac joint at the site of the previous ureterolithotomy on that side. Cystoscopy was done in an attempt to establish drainage by passing a ureteral catheter beyond the stone. The right ureteral orifice showed no efflux of urine and the ureteral catheter was obstructed at a point shown by the x-ray to be 1.5 cm. below the calculus. After a retrograde pyelogram was attempted the diagnosis was established of a ureteral calculus impacted at the site of a postoperative stricture of the lower third of the right ureter. Because of the obvious difficulty of operating on a ureter encased in scar tissue and made friable by edema, it was decided that definitive surgery could best be done after urinary drainage had been first established to permit the congestion to subside.

Accordingly, a right pyelostomy was performed under spinal anesthesia. The renal pelvis was markedly distended with about 60 cc of murky urine from which *Aerobacter aerogenes* and *Bacillus proteus* were cultured. Antibiotics were given and the patient had an uneventful postoperative course.

Ten days later the removal of the calculus and repair of the stricture of the ureter were carried out transperitoneally under spinal anesthesia. A muscle-splitting right rectus incision was made from the symphysis to the level of the

umbilicus. After the bowel was packed away the calculus was readily found several centimeters below the iliac vessels. Primarily by sharp dissection the scar tissue on the peritoneal side of the ureter was excised for a distance of about 5 cm., exposing the strictured segment of the ureter. A ureterotomy 4 cm. long was made through the strictured area and a hard brown calculus, 1.5 cm. in its longest axis, was removed. A second incision was made slightly higher up in the ureter, through which a 10F latex catheter was passed down the ureter as a splint and a 12F latex catheter passed up to the kidney for drainage. Both catheters and a Penrose drain were brought out extraperitoneally through stab incisions. The splinting catheter was loosely fixed to the opened ureter with several fine sutures of plain catgut as described by Davis.<sup>11</sup>

The edges of the peritoneum about the ureterotomy could not be brought together because the peritoneum had been excised along with the scar tissue and the adjacent peritoneum was so fixed in the scar tissue that it could not be mobilized for suture. Since any attempt to raise peritoneal flaps would have endangered the vessels, and since the sigmoid was not sufficiently mobile to be used on the right side, we were forced to free the caecum and ascending colon sufficiently to bring them down to cover the peritoneal defect, suturing them in place with 00 chromic catgut. As an outlet for any urinary leakage that might seep into the peritoneal cavity a Penrose drain was led out from the rectovesical pouch through the lower end of the laparotomy incision. After silk tension sutures had been placed, the peritoneum was closed with 0 chromic doubled, the rectus fascia with 0 chromic interrupted sutures, and the skin with fine cotton. The antibiotics were continued after the operation.

The patient had an uneventful course and at no time was there any evidence of peritonitis or intestinal obstruction. The temperature never went above 99.8F. The intraperitoneal drain was removed on the second postoperative day and the extraperitoneal drain on the thirteenth day. The pyelostomy tube was taken out on the twenty-fourth day and the ureterostomy catheters 2 days later; neither was followed by any pain, fever, or urinary leakage.

#### DISCUSSION

Certain technical points in celiotomy for surgery of the lower ureter should be considered. Although the operation is simple in concept, certain maneuvers may sometimes be essential to insure success. Both Eisendrath and Sweetnam used the Trendelenburg position, and the latter states that he had his patients so placed before beginning the operation. It was our belief that such a procedure leaves a calculus free to slip loose and migrate back up to the kidney while the surgeon is making his way through the abdominal wall. We felt that it was better to keep the patient flat until the ureter had been secured with a Babcock clamp placed above the level of the stone.

No hard and fast rule can be set for the necessity for urinary diversion nor the technique to be used for this purpose. When such a procedure is desired pyelostomy or ureterostomy drainage seems desirable. In addition to the pyelostomy

<sup>11</sup> Davis, D. M.: Intubated ureterotomy. *J. Urol.*, 57: 233, 1947.

we had planned to use a T-tube ureterostomy, but could find none with an arm long enough to splint the entire strictured segment of the ureter. Instead we used the two latex catheters after the manner of Mullenix and Prentiss.<sup>12</sup> The catheter passed to the kidney drained a large amount of urine, indicating that the pyelostomy did not act as a complete by-pass. Dick does not describe his method of drainage.

The necessity for the intraperitoneal Penrose drain might be questioned. In operating for perforated duodenal ulcer Bailey<sup>13</sup> placed a pelvic drain through a suprapubic stab incision. We thought that we should provide an outlet for any urine that might leak into the peritoneal cavity and would naturally gravitate to the pelvic pouch. The peritoneal closure should be sufficiently water-tight after two or three days to permit the withdrawal of the drain at that time. If necessary the drain may be left in place as long as there is urinary drainage. In our case the drain yielded no urine.

Much emphasis has been placed in the literature on the prevention of urinary chemical peritonitis, but the danger of later intestinal obstruction seems to have been overlooked. Careful closure of the pelvic peritoneum is a safeguard against both these complications. It is unlikely that after a secondary operation any intestine could herniate through this defect, buttressed as it is by dense scar tissue, but inadequate closure leaves a bare area which invites adhesions and small bowel obstruction. Dick was able to suture the pelvic peritoneum accurately in each of his cases, but we were not so fortunate and the closure had to be improvised. It can be done with a free graft of omentum or by covering the defect with caecum or sigmoid which is sutured to the pelvic peritoneum. The fixation of the mobilized colon should be snug enough to prevent the formation of recesses into which small bowel might herniate. Adequate mobility of either segment of the large bowel can be obtained by incising its lateral peritoneal leaf.

#### SUMMARY

A review of the literature and the case reported here indicates the value and the relative safety of the transperitoneal approach for the surgery of selected lesions of the lower ureter. The antibiotics and the adequate extraperitoneal diversion of the urine make the procedure feasible even in infected cases. Some technical aspects are discussed and the procedure is recommended particularly for secondary operations upon the ureter, where the extraperitoneal dissection promises to be difficult and hazardous.

416 Marlborough St., Boston, Mass. (B. R. S.)

384 Post St., San Francisco, Calif (J. W. S.)

<sup>12</sup> Mullenix, R. and Prentiss, R.: Ureteral injuries. *J. A. M. A.*, 145: 1244, 1951.

<sup>13</sup> Bailey, H.: *Emergency Surgery*. Baltimore: Williams & Wilkins, 1944, 5th ed., p. 135.

## TUMORS OF THE URETER

WILLIAM J. BAKER AND EDWIN C. GRAF

*From the Urological Services of St. Luke's Hospital and Cook County Hospital, Chicago, Ill.*

The incidence of ureteral tumors has been on the increase proportionate with the education of the doctors and better methods of diagnosis. There are now more than 200 reported instances of this entity in medical literature. This study is intended to review and to summarize the clinical courses of 17 patients in whom the diagnosis of ureteral tumor was established by histopathological examination. One of these patients was reported previously. Another of the patients had a metastatic lesion of the ureter. Thus, 15 patients are added to the published list of primary ureteral tumors.

### CASE REPORTS

*Case 1.* Mr. N. N., 64 years of age, was admitted to the hospital on May 15, 1947. The patient had noted intermittent hematuria for 9 months but he neglected to present himself for treatment. His past history was pertinent. Bladder tumors were fulgurated cystoscopically seven years before the present admission. Fulguration of bladder tumors was repeated 2 years later. Physical examination was entirely normal. Urine cultures were negative. Cystoscopic examination revealed tumor tissue protruding from the left ureteral orifice. Ureteral catheters were passed and retrograde pyelograms were made (fig. 1). A filling defect was noted in the lower end of the left ureter which was associated with a left hydro-ureteronephrosis. Nephro-ureterectomy was performed on May 19, 1947. Examination of the surgical specimen revealed marked dilatation of the major and minor calyces and the attached ureter. A soft grey papillary tissue lined the distal 2.5 cm. of the ureter (fig. 2). Histological examination of the tumor showed papillary carcinoma (fig. 3). The patient made an uneventful recovery and is living and well four years after surgery. Observation cystoscopy was performed in May of 1949 and no tumor was present.

*Case 2.* Mrs. L. W., 79 years of age, was admitted to the hospital on November 21, 1948. Vesical papillomatosis had been controlled by transurethral fulguration during the preceding 6 years. She was advised to enter the hospital for urological study when routine office cystoscopy revealed a bloody efflux from the right ureteral orifice. A mass was noted in the right upper abdominal quadrant on physical examination. Cystoscopy was performed and retrograde pyelo-ureterograms were made. The right ureter was obstructed at 12 cm. The x-ray revealed a hydronephrosis of the right kidney with marked ureterectasis (fig. 4, A). The left kidney and ureter were normal. Right nephro-ureterectomy was performed on November 26, 1948. Marked dilatation of the calyces, the renal pelvis, and the ureter was found. The distal 9 cm. of the ureter had a velvety, granular surface and the wall of the ureter was 8 mm. thick at this level (fig. 4, B). Microscopic study revealed papillary carcinoma. The postoperative course was uneventful.

Accepted for publication May 23, 1952.

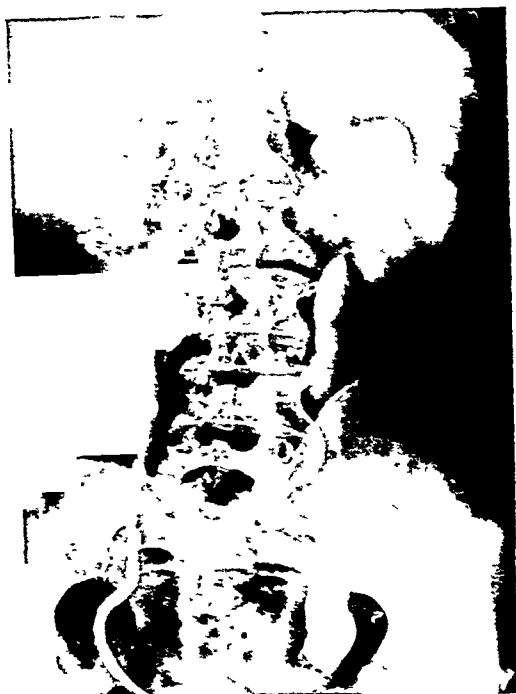


FIG. 1. Case 1 Left hydro-ureteronephrosis proximal to filling defect in lower end of left ureter.



FIG. 2 Case 1 Papillary carcinoma in lower end of ureter had caused hydro-ureteronephrosis.



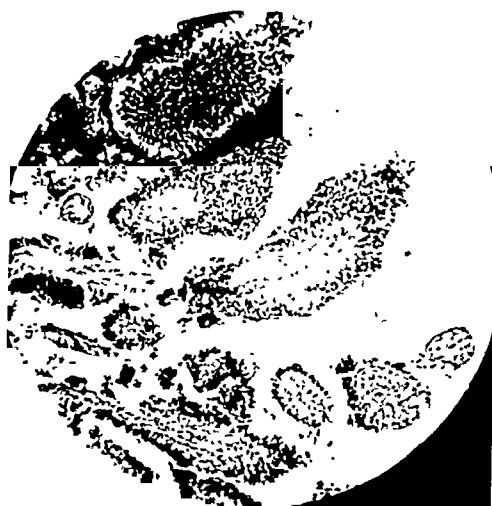


FIG. 3. Case 1. Papillary carcinoma of ureter

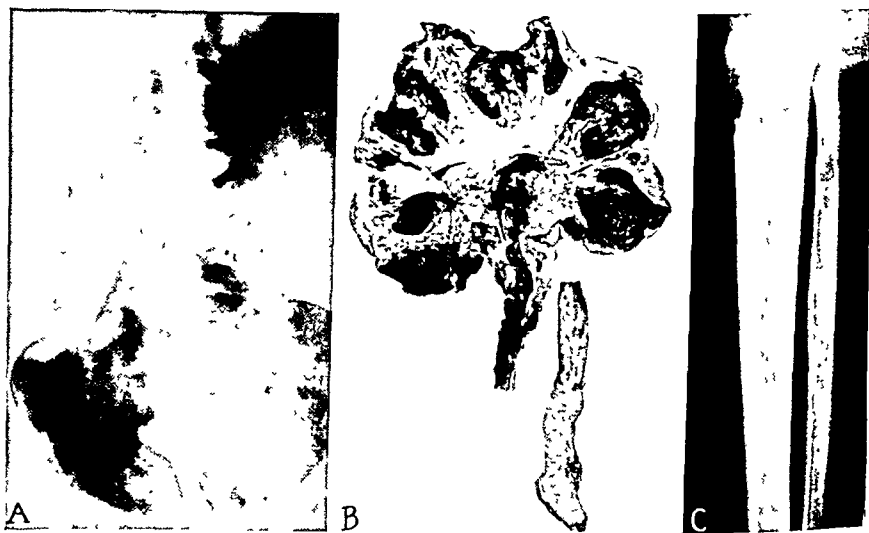


FIG. 4. Case 2. *A*, ureterectasis proximal to filling defect of right lower ureter. *B*, Surgical specimen. Tumor involved lower 9 cm. of ureter. *C*, invasion in upper part of tibia.

except for pain in the left tibia. X-ray examination demonstrated a lesion (fig 4, *C*). Biopsy proved it to be a metastatic lesion from the bladder or ureter. The patient failed rapidly and died 7 months after surgery.

Case 3. Miss J. B., 75 years of age, was hospitalized on October 23, 1947. She had been hospitalized in 1937 for cystoscopic fulguration of bladder tumors. Recurrences of the papillomas were fulgurated in 1942 and again in 1946. Hospitalization was advised on the present occasion because a mass was noted in the left upper abdominal quadrant on routine office examination. Physical examination was essentially negative except for the abdominal findings. Urological study revealed an obstruction of the left ureter at 4 cm. X-ray studies demonstrated an unusually dilated and tortuous left ureter which was marked by numerous filling defects. The left renal pelvis was not visualized (fig. 5, A). Left nephroureterectomy was performed on October 27, 1947. There was marked hydronephrosis of the kidney. The widely dilated ureteral lumen was lined by grey-red



Fig. 5 Case 3. A. Filling defect of lower aspect of ureter. B. gross specimen. Entire ureteral lumen lined by tumor.

nodular tissues (fig. 5, B). Histopathological study revealed papillary carcinoma of the ureter and marked atrophy of the renal parenchyma. The patient is alive and well 4 years after surgery.

Case 4. Mr. J. B., a 61 year old white man, was admitted to the hospital on September 15, 1948. He complained of hematuria and frequency at intervals during the preceding month. This patient had been treated in 1938 for bladder tumors. A recurrence of the tumors necessitated fulguration in 1943. He had no urinary complaints between 1943 and the present episode of hematuria and frequency. Physical examination was entirely normal. Cystoscopy was performed. Tumor tissue protruded from the right ureteral orifice. Catheterization of the right ureter was not successful. Excretory urograms revealed a non-visualizing right kidney. The left kidney and ureter were normal. Right nephroureterectomy, including a cuff of bladder, was performed on September 18, 1948



FIG. 6. Case 4 Surgical specimen. Tumor has caused occlusion of lower ureter and hydro-ureteronephrosis.

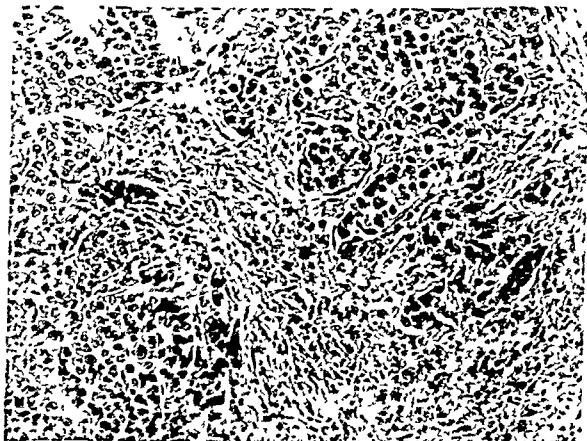


FIG. 7. Case 4 Squamous cell carcinoma of ureter

The surgical specimen showed a hydro-ureteronephrosis and a tumor occluding the lower aspect of the ureter (fig. 6). Microscopic study revealed squamous cell carcinoma (fig. 7). The carcinoma became disseminated widely. The patient died within 6 months.

*Case 5.* Miss J. E. 73 years of age, was admitted to the hospital on August 13, 1950. The immediate cause for hospitalization was the presence of a large mass which was found to fill the entire left half of the abdomen. She had been seen at fairly regular intervals during the preceding 11 years. Innumerable papillomas had been fulgurated through the years. She tolerated instrumentation fairly well and cystoscopy had become a routine matter with her. Physical examination was negative except for the mass in the left side of the abdomen. Cystoscopy revealed a tumor overlying the region of the left ureteral orifice. The tumor was resected and the left ureteral orifice was visualized. Retrograde pyelograms demonstrated an enormously dilated left kidney and ureter. An obstruction at



FIG. 8. Case 5. Enormous dilatation of left ureter

the level of the fifth lumbar vertebra caused the ureteral catheter to coil upon itself in the dilated lower segment of the ureter (fig. 8). Nephro-ureterectomy was performed on August 18, 1950. Recovery following the surgery was prompt. The specimen consisted of a markedly dilated kidney pelvis and ureter (fig. 9). At the lower end of the ureter in the lining were soft grey tissues that extended 2 cm. in the length of the lumen and reached around the lumen. Histologic study disclosed papillary carcinoma of the ureter. Post-operative radiation therapy and the results of years of fulguration caused the bladder to be contracted. A right dermal ureterostomy was performed on March 21, 1951, to divert the urine and offer relief to a miserable existence. Although the ureterostomy functioned well, the patient's general condition deteriorated and she expired two months later. Autopsy was performed, and extensive carcinomatosis was found.

*Case 6.* Mr. P. E., 57 years of age, was admitted to the hospital on November 6, 1948. He stated that he had painless hematuria for 6 months. Weakness and lassitude were present for 1 month. Physical examination was entirely negative. Cystoscopy revealed a normal bladder. The ureters were catheterized without obstruction but a hydronephrotic drip of clear urine was noted on the left. Retrograde pyelograms revealed a left hydro-ureteronephrosis to the level of the top of the sacrum (fig. 10). Ebonization of the fourth lumbar vertebra later proved to be a metastasis. Left nephro-ureterectomy was performed on November 16, 1948. The left kidney and ureter were greatly dilated to a point 8.5 cm. above the lower end of the ureter. At this point there was marked thickening of the ureteral

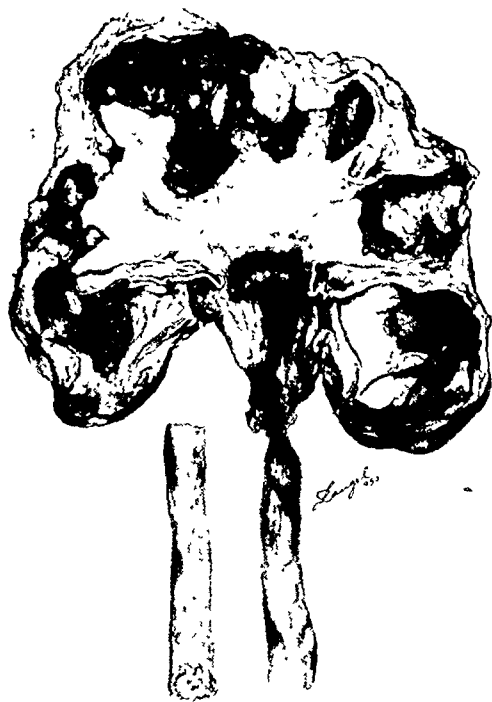


FIG. 9. Case 5. Occlusion of lumen of ureter has been caused by tumor

wall which caused a constriction at this level (fig. 11). Below this constriction the caliber of the ureter was normal. Microscopic study revealed squamous cell carcinoma. The patient recovered from the surgery without incident but he failed rapidly and died from metastases one year after surgery.

*Case 7.* Mr. L. S., a 54 year old white man, was admitted to the hospital in December 1949. He was admitted to a medical ward complaining of severe dyspepsia. Physical examination revealed a mass in the upper right abdominal quadrant. Cystoscopy revealed a normal bladder. The right ureter was obstructed at 8 cm. Repeated attempts to catheterize the right ureter using general anesthesia as an aid for relaxation were regularly unsuccessful. Retrograde injection of radio-opaque dye failed to visualize the right ureter or kidney proximal to the

obstruction. The left ureter and renal pelvis were normal according to x-ray study. Excretory urograms failed to visualize the right kidney or ureter. The preoperative diagnosis was obstruction of the ureter by a non-opaque calculus. The right kidney and ureter were exposed through a right lumbar incision in January 1950. The mass was found to be a hydronephrotic kidney. The dilated ureter was followed to a cartilaginous fusiform swelling at the level of the bifurcation of the common iliac artery. There was no remarkable fixation of the ureter at this point. A nephro-ureterectomy, including a cuff of the bladder, was

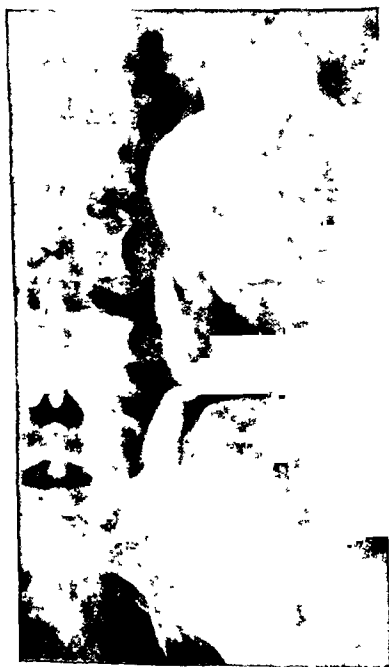


FIG. 10

FIG. 10. Case 6. Left hydro-ureteronephrosis. Ureteral obstruction noted. Ebonization of fourth lumbar vertebra present.

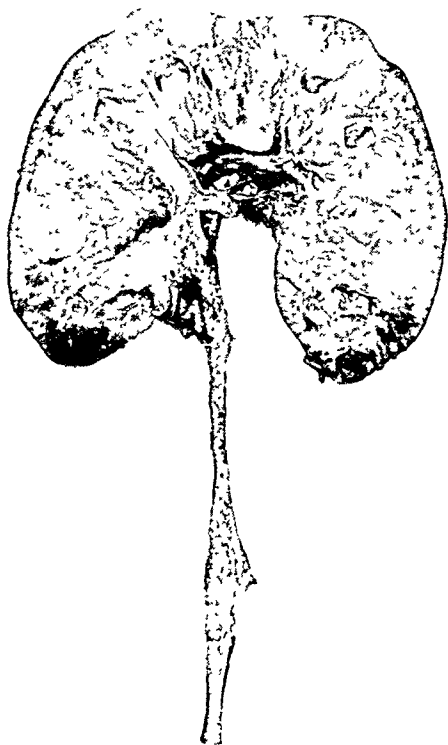


FIG. 11

FIG. 11 Case 6. Surgical specimen. Tumor noted at junction of middle and lower thirds of ureter.

performed. Pathological study revealed that the fusiform swelling was caused by a fleshy tumor (fig. 12) Microscopic examination showed a papillary carcinoma of the ureter. The patient made an uneventful recovery and is alive and well eighteen months after surgery.

*Case 8.* A white man, 40 years of age, was admitted to the hospital on February 13, 1950, on the service of Dr. Harlan English, Danville, Ill. The patient complained of vague distress in the right flank for some time and profuse painless hematuria of 24 hours' duration. Cystoscopic study and pyelographic study were made the morning of his admission to the hospital. The pyelogram revealed

*Case 6.* Mr. P. E., 57 years of age, was admitted to the hospital on November 6, 1948. He stated that he had painless hematuria for 6 months. Weakness and lassitude were present for 1 month. Physical examination was entirely negative. Cystoscopy revealed a normal bladder. The ureters were catheterized without obstruction but a hydronephrotic drip of clear urine was noted on the left. Retrograde pyelograms revealed a left hydro-ureteronephrosis to the level of the top of the sacrum (fig. 10). Ebonization of the fourth lumbar vertebra later proved to be a metastasis. Left nephro-ureterectomy was performed on November 16, 1948. The left kidney and ureter were greatly dilated to a point 8.5 cm. above the lower end of the ureter. At this point there was marked thickening of the ureteral

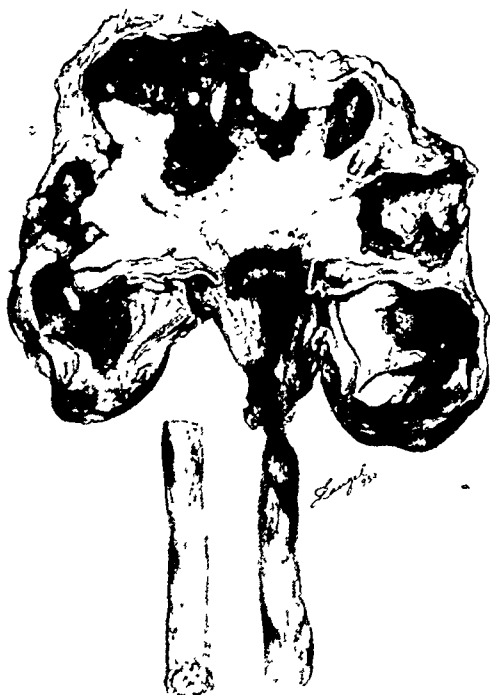


FIG. 9. Case 5. Occlusion of lumen of ureter has been caused by tumor

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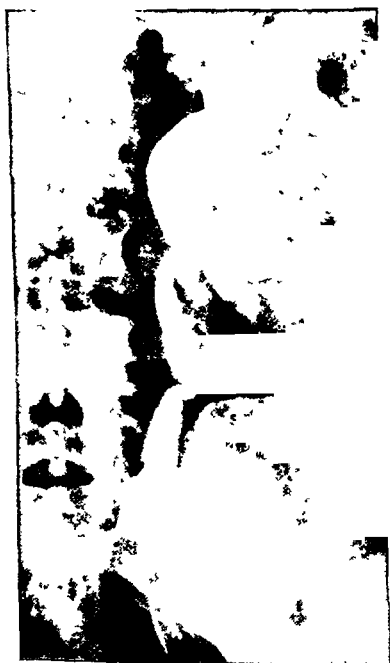


FIG. 10

FIG. 10. Case 6. Left hydro-ureteronephrosis. Ureteral obstruction noted. Ebonization of fourth lumbar vertebra present.

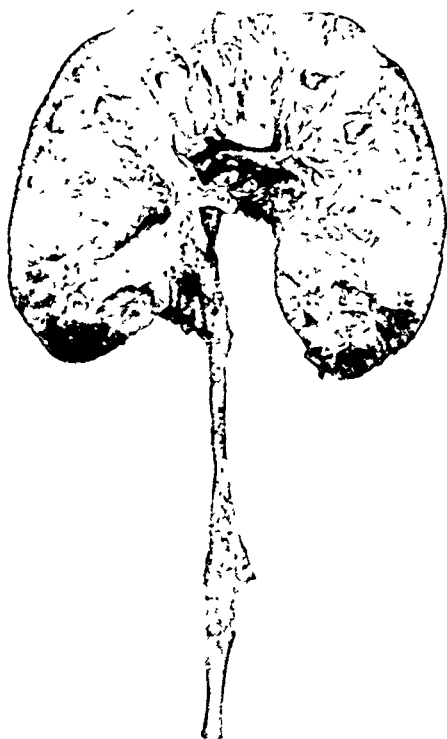


FIG. 11

FIG. 11 Case 6. Surgical specimen. Tumor noted at junction of middle and lower thirds of ureter.

performed. Pathological study revealed that the fusiform swelling was caused by a fleshy tumor (fig. 12) Microscopic examination showed a papillary carcinoma of the ureter. The patient made an uneventful recovery and is alive and well eighteen months after surgery.

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rather conclusive evidence that the patient had a tumor in the lower end of his right ureter (fig. 13). On April 12, 1950, a right nephro-ureterectomy was done and the intramural portion of the ureter was removed. Microscopic study revealed papillary carcinoma of the ureter with no evidence of penetration of the muscular layer. The postoperative course was uneventful. Cystoscopic observation on June 9, 1951, revealed a normal bladder. His general condition was excellent.

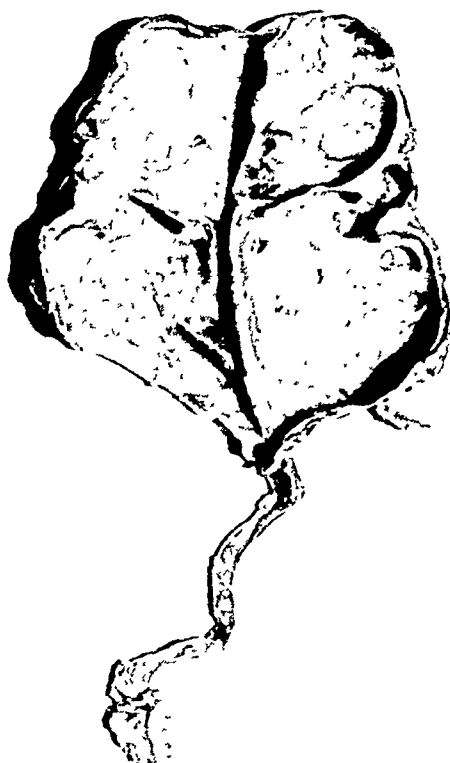


FIG. 12. Case 7. Surgical specimen. Giant hydronephrosis caused by tumor in lower third of right ureter.

*Case 9.* Mrs. O. L., 36 years of age, was hospitalized for study on August 7, 1946. She complained of intermittent severe pain in the left flank which radiated to the left groin. The past history included the occurrence of massive painless hematuria 8 years ago. The bleeding stopped spontaneously, and no studies were made. Physical examination was negative. Cystoscopic study revealed a normal bladder. The left ureter was obstructed at 25 cm. The retrograde pyelogram demonstrated a hydro-ureter below the site of the obstruction but no dye was found to enter the left renal pelvis (fig. 14, A). The right kidney and ureter were normal. Left nephro-ureterectomy was performed on August 12, 1946. Pathological examination of the specimen showed a relatively normal left kidney. Attached by a pedicle (fig. 14, B) at a level approximately 15 cm. below the ureteropelvic junction was a long grey polyp that hung in the lumen for a distance

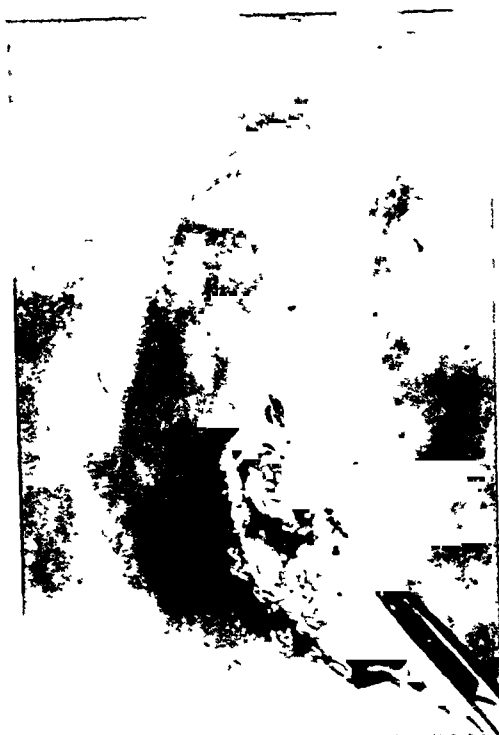


FIG 13 Case 8 Gross specimen Ureteral tumor

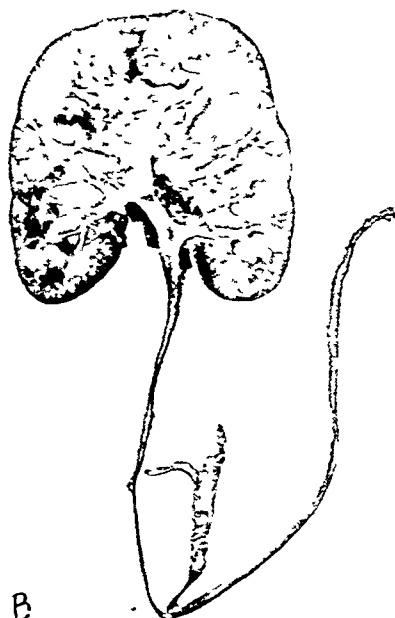


FIG 14 Case 9 A, x ray Hydro ureter noted below ureteral obstruction on left. Right ureter and kidney normal. B, surgical specimen. Polyp attached by narrow pedicle and hung loosely in ureteral lumen.

of 9 cm. Microscopic examination revealed a moderately edematous and vascular fibrous stroma with the surface edge covered by transitional epithelium corresponding to that epithelium lining the ureter. The patient is alive and well five years postoperatively.

*Case 10.* Mr. C. F., 37 years of age, was admitted to the hospital for study on August 9, 1944. His only symptom was painless hematuria on the day before admission to the hospital. The physical examination was entirely normal. Urological examination revealed a normal bladder. Catheterization of the left ureter revealed obstruction at 22 cm. The retrograde pyelograms showed a filling defect



FIG. 15: Case 10. A, x-ray demonstrated filling defect in middle third of left ureter. B, gross specimen. Ureteral polyp.

in the middle third of the left ureter (fig. 15, A). Surgical exploration was performed on August 12, 1944. A one inch incision was made in the ureter at the proximal aspect of a fusiform swelling of the middle one-third of the ureter. A polyp, 7 cm. in length, was extracted from the lumen of the ureter (fig. 15, B). The polyp was excised and its base was thoroughly fulgurated. The ureter was repaired with interrupted 00 catgut sutures. The pathological diagnosis was mucosal polyp of the ureter. Sections showed markedly edematous fibrillar stroma. The surface was covered by transitional cell epithelium. The post-operative course was uneventful. The integrity of the left kidney and ureter has been checked each year with intravenous pyelograms. The pyelograms have been normal and the patient remains in excellent health seven years after surgery.

*Case 11.* Mrs. H. O., a 35 year old married, white woman, entered the hospital complaining of severe colicky pain in the left side of the abdomen and back. She also noted hematuria. These symptoms were present, intermittently, during the preceding 2 years. A left nephrectomy had been performed 3 weeks before the present admission. The symptoms had continued unabated. The pathological diagnosis was chronic nephritis. Cystoscopic examination revealed a blood clot which protruded from the left ureteral orifice. A ureteral catheter was passed on the left and drained bright, red blood. An ureterogram revealed a normally



FIG 16. Case 11. Ureteral polyps

constituted left ureter. The preoperative impression was carcinoma of the ureter. The ureter was excised. Pathological study revealed three distinct tumors arising from the mucosa of the ureter (fig. 16). Microscopic examination revealed that these tumors were polyps and no malignant tendency was found. The patient made a rapid recovery and was living and well 10 years after surgical excision of the left ureter.

The preceding case was reported by Dr Harry Culver in the *Journal of Urology* 6: 331 (Oct.) 1921.

*Case 12.* Mr. E. L., a 57 year old white man, was admitted to the hospital

on June 2, 1948. He had many episodes of hematuria during the past year. Urgency and frequency were associated with these attacks of hematuria. A left nephrectomy had been performed 25 years before the present admission. The diagnosis was calculous pyonephrosis. There were no positive physical findings. Cystoscopic examination revealed a bulging, dusky red, left ureteral orifice which was exuding blood. Surgery was performed on June 3, 1948. Cystotomy was done and the bulging segment of bladder was circumcised and resected from the bladder. The contiguous 19 cm. of the left ureter were dissected and removed



FIG. 17

FIG. 17. Case 12. Surgical specimen included bladder surrounding left ureteral orifice and 19 cm. of ureter.



FIG. 18

FIG. 18. Case 13. Surgical specimen. Excised ureteral stump contained papillary carcinoma.

with the segment of bladder (fig. 17) Examination of the ureter revealed that the lower 7 cm. of lining mucosa was replaced by masses of soft, grey-red tissue, singly and confluent, ranging to about 1 cm. in diameter and covering about 70 per cent of the surface. Similar tissues were found, less extensively, throughout the ureter. Histologic study demonstrated papillary carcinoma. The postoperative morbidity was severe and protracted but he made a complete recovery and is living and well 3 years after surgery.

*Case 13.* Mr. W. C., 50 years of age, was admitted to the hospital on December 7, 1946. Two days before admission the patient noted a mass in the region of a left lumbar surgical incision. He had no other symptoms or findings. The past

history was pertinent in that a left nephrectomy had been performed 3 years before admission. The diagnosis was calculous pyonephrosis. One year before the present admission a left ureterectomy was performed. The diagnosis was papillary carcinoma of the ureter (fig. 18). The microscopic pathology was papillary carcinoma. Abdominal examination revealed a mass about the size of a grapefruit in the left costovertebral region at the site of the well healed surgical incision. The mass was fixed; it was firm in consistency and smooth in contour. Excision of the mass which was found to be a hemorrhagic cyst, was performed on December 10, 1946. On the lining side there were some granular tissues. In one place there was a mass 1.5 by 1.3 by 1 cm. Histologic examination of this tumorous mass revealed papillary carcinoma which closely resembled papillary carcinoma of the urothelium. Recovery was prompt following surgery. Subsequently, metastases occurred to the inguinal and axillary lymph glands and the patient expired about one year later.

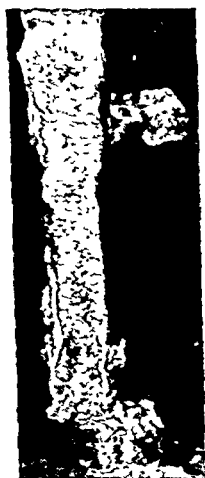


FIG. 19. Case 14. Surgical specimen. Excised ureter contained tumor

*Case 14.* Mr. P. M., a 48 year old white man, was admitted to the hospital in March 1942. He was a hotel cook by trade. Past history included a nephrectomy in 1937 at another hospital. The records of this hospital were surveyed by us and the pathological report described a calculous pyonephrosis. None of the ureter had been removed. He remained in good health until the fall of 1941. He then noted painless hematuria. Retrograde urological study revealed a constant trickle of blood which poured from the left ureteral orifice. Closer inspection revealed a small tumor which protruded from this orifice. Cystoscopic biopsy showed this protruding tumor to be a papillary carcinoma of the ureter. Retrograde urograms were made but the left ureteral stump could not be visualized. The right ureteropyelogram was normal, and the function of this kidney was normal. Spinal anesthesia was used and the left ureter was excised from the stump of the renal pedicle to and including a cuff of the urinary bladder. Figure 19 shows the ureteral lumen to be entirely filled from one end to the other with

papillary carcinoma. His postoperative course was uneventful. Severe pain along the course of the left ureter occurred about nine months later. A frozen mass could be palpated along the left psoas gutter. This massive local recurrence of tumor was fatal just one year after the removal of the ureteral stump.

*Case 15.* Mr. H. S., a white man, 65 years old, was admitted to St. Luke's Hospital April 19, 1939. He had suffered acute sudden pain in the right lower abdominal quadrant a few hours previously. There was nausea and bladder irritability. A plain urogram revealed a calcific pea sized shadow along the course of the right ureter in its lower third just below the pelvic brim. The urine contained many red cells. The pain persisted. A retrograde urological study was done.



FIG. 20. Case 15. X-ray demonstrated opaque shadow in lower right ureter

The right ureter could not be catheterized beyond the point of the calcific shadow (fig. 20). This patient weighed almost 250 pounds. He did not pass his stone spontaneously and his pain became more acute and almost continuous. He entered another hospital where we exposed the lower right ureter on April 21, 1939. At the junction of the middle and lower thirds of the ureter, there was a hard, fixed, spindle swelling about two inches long. The lower half of the ureter with a good cuff of the urinary bladder was excised and a dermal ureterostomy was done. A right nephrectomy was performed in May 1939. The spindle shaped swelling was squamous cell cancer of the ureter which contained many calcific areas which had given the appearance of a ureteral calculus. There was extension of the cancer cells into the peri-ureteral tissues. In November 1939, he noted painless hematuria. Observation cystoscopy revealed papillary tumors in the

posterior urethra and the region of what had been the right ureteral orifice. All of the tumors were fulgurated transurethrally. This same procedure was repeated on April 24, 1941. He suffered a metastatic death in July 1941, about fifteen months after the appearance of his first symptoms.

*Case 16.* Mr. C. C. was admitted to the hospital in May 1927. He complained of intermittent painless hematuria, which had been present for several weeks. There was a weight loss of 15 pounds. Retrograde urological study showed the blood to come from the left ureteral orifice. The function of the left kidney was



FIG 21. Case 17 Obstruction of left ureter which caused hydro-ureteronephrosis

less than that of the right kidney when measured with intravenous phenol-sulfonphthalein. Catheters were passed up both ureters readily. The ureteropyelograms showed a filling defect at the junction of the middle and lower thirds of the left ureter. There was minimal hydronephrosis. A left ureteronephrectomy was done. The ureteral lesion was a squamous cell cancer which involved the entire thickness of the ureteral walls for about two inches. His postoperative progress was uneventful. He remained well and gained weight until March 1930. He then had pain in his left lower abdominal quadrant and weight loss. An exploratory operation revealed local recurrence of his cancer in the lower left psoas gutter. He died in May 1930, three years from the time of his original diagnosis.

*Case 17.* P. W., a 49 year old white man was admitted to the hospital on June



16, 1947. The presenting complaint was severe, non-radiating, dull pain in the left flank which recurred intermittently during the past 2 months. He had no urinary symptoms. His past history was pertinent. A cervical lymph node had been excised in March 1943. A recurrence of a mass in the same site was biopsied on May 15, 1947. The pathological diagnosis was highly anaplastic, metastatic carcinoma. Abdominal examination revealed a mass in the left upper quadrant which was freely movable and only slightly tender. Urine cultures were negative. Urological study revealed a marked, left hydro-ureteronephrosis which ended abruptly at the junction of the middle and lower thirds of the ureter (fig. 21). Nephro-ureterectomy was performed on June 23, 1947. A retroperitoneal mass was found at the brim of the pelvis. The mass was firmly adherent to the iliac

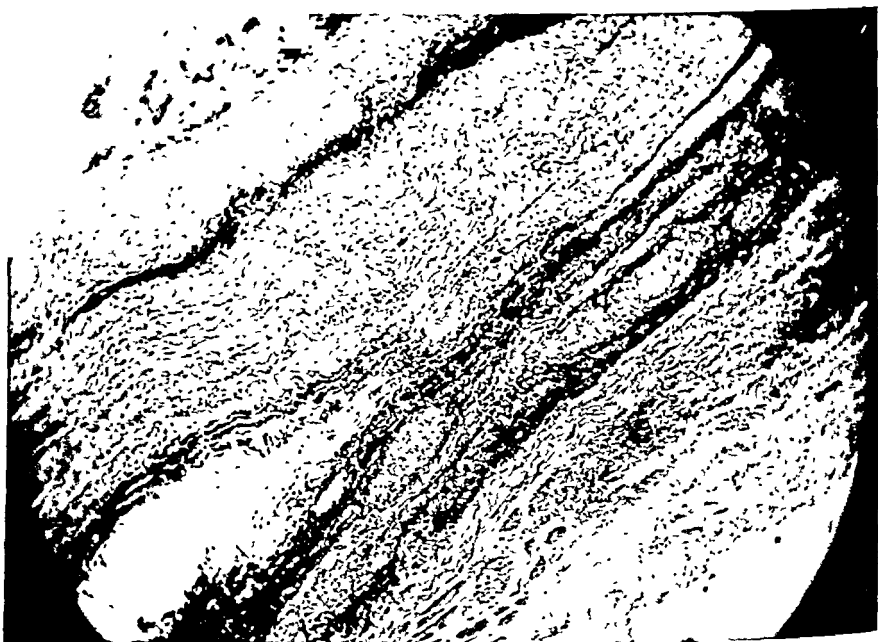


FIG. 22. Case 17. Invasion of ureteral wall by sarcoma

blood vessels, and it caused occlusion of the ureter at that level. The ureter was extricated from the mass and the kidney and ureter were removed in toto. Pathological examination demonstrated marked dilatation of the renal pelvis and upper portion of the ureter. A stricture 2.5 cm. in length greatly reduced the lumen of the ureter at the distal aspect of dilated segment of the ureter. Microscopic examination of the stricture tissues revealed invasion of the ureter by lymphosarcoma (fig. 22). The immediate course was satisfactory. The patient expired 15 months after surgery.

Pertinent facts in the clinical histories of these patients have been assembled on table 1. The patient with the metastatic lesion to the ureter has been excluded from the chart. Eleven of the sixteen patients were men. The incidence agrees with other series of ureteral tumors. Eleven of the sixteen tumors involved the

ft ureter. The lower segment of the ureter was most commonly involved. The three benign tumors were found in the middle third of the ureter. This location makes the benign tumor more accessible and enhances the prospects of local resection. Conservative surgery is especially desirable for the benign tumors since they occur in the younger age group. The three patients were 36, 37 and 35 years of age. Papillary carcinoma was the predominant type of tumor. Ten of the sixteen tumors were papillary, four were squamous cell carcinoma and three were the so-called benign mucosal polyps. Five of the patients gave a history of bladder tumor. An important lesson to be appreciated from this review has been recently emphasized by Ewart. He stated, "If tumors are present in the bladder the urologist must prove that the upper urinary tract is not also a site of tumors." He further recommends excretory urograms each year in the presence of papillomas

TABLE 1

| NO. | AGE | SEX | SIDE | SITE   | PATHOLOGY     | SURVIVAL      | HISTORY OF<br>BLADDER<br>TUMOR | PREVIOUS<br>NEPHREC-<br>TOMY |
|-----|-----|-----|------|--------|---------------|---------------|--------------------------------|------------------------------|
| 1   | 64  | M   | L    | Lower  | Papillary Ca. | Alive— 4 Yrs. | Yes                            | No                           |
| 2   | 79  | F   | R    | Lower  | Papillary Ca. | Dead— 9 Mos.  | Yes                            | No                           |
| 3   | 75  | F   | L    | Total  | Papillary Ca. | Alive— 4 Yrs. | Yes                            | No                           |
| 4   | 61  | M   | R    | Lower  | Squamous Ca.  | Dead— 6 Mos.  | Yes                            | No                           |
| 5   | 73  | F   | L    | Lower  | Papillary Ca. | Dead— 9 Mos.  | Yes                            | No                           |
| 6   | 57  | M   | L    | Middle | Squamous Ca.  | Dead— 1 Yr.   | No                             | No                           |
| 7   | 54  | M   | R    | Lower  | Papillary Ca. | Alive— 2 Yrs. | No                             | No                           |
| 8   | 40  | M   | R    | Lower  | Papillary Ca. | Alive—18 Mos. | No                             | No                           |
| 9   | 36  | F   | L    | Middle | Polyp         | Alive— 5 Yrs. | No                             | No                           |
| 10  | 37  | M   | L    | Middle | Polyp         | Alive— 7 Yrs. | No                             | No                           |
| 11  | 35  | F   | L    | Middle | Polyp         | Alive—10 Yrs. | No                             | Yes                          |
| 12  | 57  | M   | L    | Total  | Papillary Ca. | Alive— 3 Yrs. | No                             | Yes                          |
| 13  | 50  | M   | L    | Total  | Papillary Ca. | Dead— 1 Yr.   | No                             | Yes                          |
| 14  | 48  | M   | L    | Total  | Papillary Ca. | Dead— 1 Yr.   | No                             | Yes                          |
| 15  | 65  | M   | R    | Lower  | Squamous Ca.  | Dead—15 Mos.  | No                             | No                           |
| 16  | 53  | M   | L    | Lower  | Squamous Ca.  | Dead— 3 Yrs.  | No                             | No                           |

of the bladder. Four of the patients either had tumor in the ureter at the time of a previous nephrectomy or developed the ureteral tumor following nephrectomy. Much has been written about the hazards of the ureteral stump. The rather high incidence of tumor in ureteral stumps in this series of patients is impressive.

#### DISCUSSION

The majority of ureteral tumors occur in the lower third of the ureter. Those that occur in the upper half of the ureter are either polyps or apparent extensions up or down the ureter. This brings up the question of transplantation of cancer cells on healthy ureteral mucosa. Investigators of pathology find it next to impossible to transplant tumor cells on the mucosa of experimental animals, unless the mucosa has been previously ulcerated or injured. For this reason, more and more clinicians believe that tumors of the bladder or kidney do not transplant themselves in the ureter. In other words, there is probably a multi-

centric agent which stimulates these tumors to appear along the urinary tract. On the whole, the ureter is fairly resistant to tumor formation.

From a pathological viewpoint, ureteral tumors can be divided into the polypoid, papillary and sessile types. The polypoid ureteral tumor is derived from the submucosal structures and is considered a benign lesion. The papillary ureteral carcinomas may contain many transitional cell cancers. The sessile ureteral tumors are usually squamous cell carcinomas and offer a very poor diagnosis. A complete pathological classification must include invading extra-urinary tumors, metastatic ureteral tumors and ureteral tumors from such entities as Hodgkins' disease. An interesting observation has been that although the embryological derivation of the ureter is mesenchymal and that of the urinary bladder is entodermal, the papillary tumors of both seem to have about the same structure. It should be kept in mind that ureteral tumors metastasize much earlier than bladder tumors. This earlier metastasis may be due to the thin wall of the ureter which forms a poor barrier to a dissemination of the tumor.

The three outstanding symptoms of the ureteral tumor are hematuria, pain and tumor mass. The hematuria has an utter lack of conformity to any definite pattern. The pain is usually from ureteral obstruction or involvement of nearby and remote structures by extension and metastases. The tumor mass is usually a large hydronephrotic kidney due to the ureteral obstruction. However, ureteral tumors have been felt from the abdominal, vaginal and rectal routes.

Diagnosis may be aided by centrifuging the urine to obtain sediment for paraffin blocks. Sections of these sediment blocks can be stained for cancer cells. The normal transitional cell of the urinary tract is sometimes confused with a true cancer cell. Plain roentgen studies are valuable to reveal bony metastases, calcified areas in the ureteral tumor and large kidney shadows of obstructed ureters.

The common findings of retrograde urological study are a marked decrease in renal function of the involved side, tumor tissue which projects from the ureteral orifice and a bulge in the ureteral ridge. Biopsy of any evident tumor is mandatory. If bleeding is due to a tumor of the upper end of the ureter, blood appears only at the ureteral orifice with ureteral peristalsis. Bleeding from a tumor in the lower end of the ureter usually appears as a continuous trickle. A ureteral catheter may pass to the kidney without causing bleeding. If the tumor is in the lower end of the ureter, slight trauma from the ureteral catheter may result in a continuous flow of blood through and around the catheter. The ureteral catheter may coil below the ureteral tumor. Retrograde ureteropyelograms may show filling defects along the ureter or spindle shaped swellings of the ureter. The character of the filling defect varies with the type, shape and extent of the growth. If there is an infiltrating sessile type of tumor present, there is also an irregular decrease in the size of the lumen for a considerable extent and this is accompanied by a dilatation of the ureter and kidney above the site of the tumor. The papillary type of tumor, if solid and pedunculated, may cause a goblet-shaped filling defect with dilatation of the ureteral lumen above and below the tumor. When there are multiple papillary tumors of the ureter present, modifications of the foregoing

picture may be seen throughout the whole length of the ureter. If the surface of the ureteral tumor is quite irregular, the filling defect may look like a brush: the so-called brush like appearance.

The treatment of ureteral tumors is a complete nephro-ureterectomy with a wide cuff of the bladder. A one stage procedure is recommended. If a two stage nephro-ureterectomy is considered, the removal of the tumor bearing area is done for the first stage. It is possible sometimes to excise a portion of the ureter with its tumor and join the ureteral ends or transplant the ureter to the bladder or renal pelvis. If conservation of the kidney is of prime importance, dermal ureterostomy or nephrostomy can be used. Roentgen and radium therapy are used for metastatic pain of ureteral tumors but not too successfully. After a complete ureteronephrectomy for ureteral tumor, periodical cystoscopic bladder observation will protect the patient from new bladder tumors. The immediate prognosis of these patients is good. No deaths occurred in the immediate post-operative period. The 5-year prognosis is bad. The 10-year prognosis is most discouraging.

#### SUMMARY

Seventeen patients have been presented in whom the diagnosis of ureteral tumor was established by histopathological study. One of these patients has been reported previously. One of the patients had a metastatic lesion of the ureter. Thus fifteen new cases of ureteral tumor are added to the literature. Pertinent facts of the clinical histories and findings have been assembled on table 1. A discussion has been offered concerning the etiology, the pathology, the symptoms and diagnosis, and the treatment of ureteral tumors.

Gratitude is expressed to Dr. Harry Culver whose interest and help facilitated this study.

7. W. Madison St., Chicago, Ill.

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## LYMPHANGIOMA OF THE URETER

F. B. JEPPESEN

Benign tumors of the ureter are rare. The number collected by various authors who have reviewed the literature varies from 32 (Edelstein and Marcus) to 68 (Vest). The great majority of these tumors are epithelial in origin. Nonepithelial tumors reported include a fibroma, neurofibroma, lipoma, myoma, and several hemangiomas. No previous mention has been found of a lymphangioma of the ureter.

### CASE REPORT

Mrs. A. S. (Hospital No. 28262), a 79 year old woman, was hospitalized October 26, 1951. Her complaint was pain in the left lower quadrant of the abdomen with radiation to her left flank and left kidney region. This pain started 5 months before admission. The first attack lasted one week and was severe enough to require sedatives. Nausea and vomiting were present. She had no fever, but gross blood was present in the urine. During the 5-month period between the onset of her trouble and her hospital admission, she had recurring attacks of pain. Eight days before admission, she had a particularly severe attack which persisted until admission. Nausea was constant and she had frequent vomiting.

Physical examination revealed a fairly well preserved white woman who was mentally alert. The blood pressure was 204/96. Heart rate was 60 and no murmurs were heard. There was no palpable mass in the left lower quadrant of her abdomen or left flank. The left kidney area was tender. The urine contained many red blood cells and a few white blood cells. Blood urea nitrogen was 9 mg. per cent.

Excretory urograms showed a moderate dilatation of the renal pelvis and calyces on the left. Fifty minutes after injection of the dye there was demonstrated wide dilatation of the left ureter, accompanied by tortuosity. This dilatation ceased rather abruptly a short distance above the bladder. The right kidney and ureter were normal.

Cystoscopy showed a normal bladder except that there appeared to be some edema around the left ureteral orifice. The only catheter that could be passed any distance up the left ureter was a size 4F with a Coudé tip. It met an obstruction several times and would only go 6 cm. Retrograde urograms showed an area of stenosis of the left ureter at its lower end which was 6 cm. in length. The stenosed area was very irregular. Above this the ureter was greatly dilated. A size 10F, acorn bulb catheter was used and a better film was obtained (fig. 1).

Diagnoses considered were a metastatic neoplasm of the ureter, diverticulitis of the colon with abscess formation, and a primary tumor of the ureter. A barium enema was normal. A gynecological consultant reported no palpable abnormality in the internal genital organs. He did feel a tender thickening in the region of the

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 21, 1952.

left broad ligament lateral to the cervix. A clinical diagnosis of a primary tumor of the left ureter was made.



FIG. 1. Left ureterogram showing stenosed area with dilated ureter above.

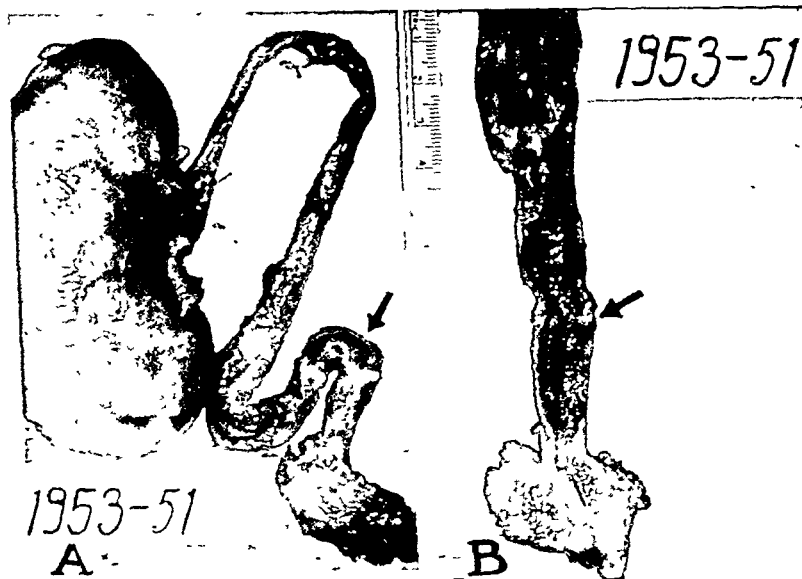


FIG. 2. A, kidney, ureter and part of bladder. B, lower ureter opened. Arrows show site of tumor nodule.

A left nephrectomy and ureterectomy were done. The tumor mass was not adherent to the surrounding tissue. It was felt as a distinct hard nodule roughly oval in shape and about two centimeters in length. Above this the ureter was dilated as shown on the x-ray film. Below the tumor nodule the ureter was dis-

tinctly larger and more fibrous than normal, but not dilated. This process extended down to the bladder. A good sized cuff of bladder tissue was removed.

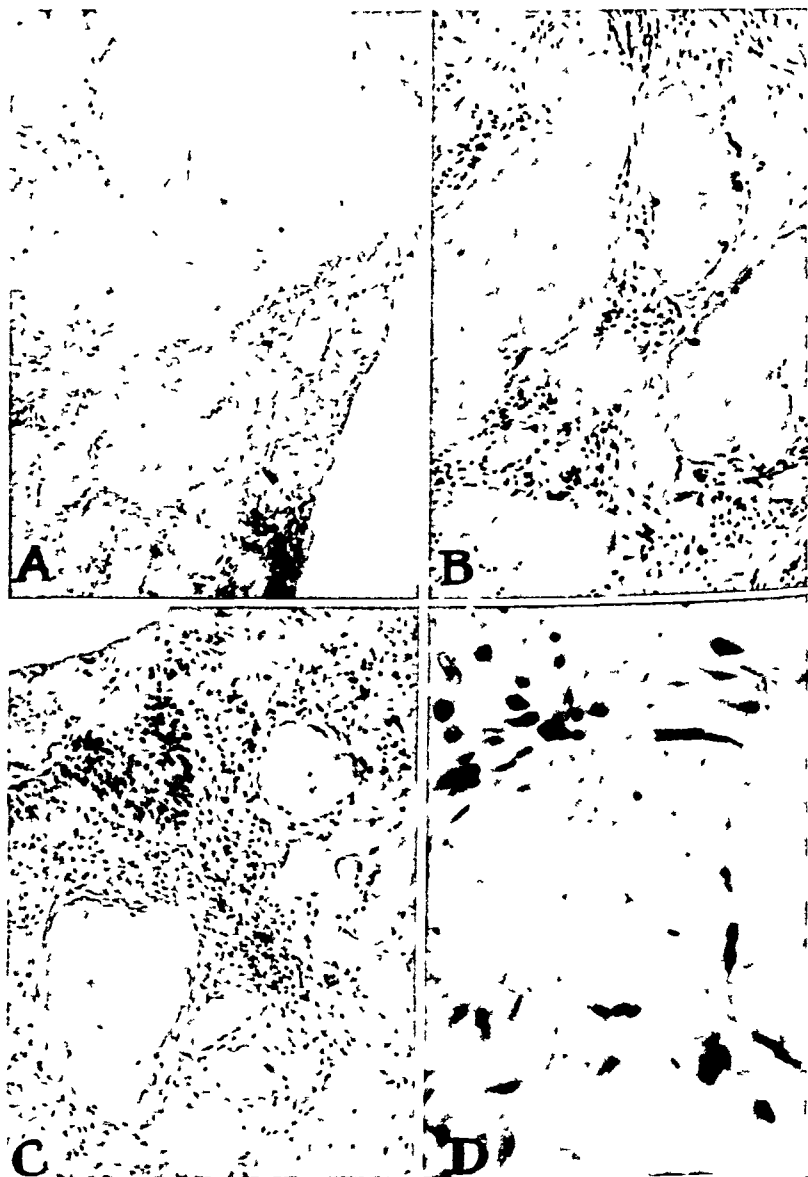


FIG 3 A one large and many small spaces filled with solidified lymph  $\times 80$  B, higher power of same field  $\times 200$  C, shows epithelial lining of ureter  $\times 200$  D, valve like formation and endothelial cells are clearly seen  $\times 800$

with the ureter (fig 2). The patient made a good recovery. She was out of bed on the ninth postoperative day and was dismissed on the nineteenth postoperative day.

The following microscopic report was made by Dr John C McCarter. "Sec

tions of the ureter at the point of greatest obstruction show the formation in and beneath the mucosa of relatively wide lymph spaces of irregular contour filled with coagulated lymph. These spaces are lined by a single layer of endothelial cells. The overlying mucosa is almost completely eroded and the surrounding tissues show some round cell infiltration. Sections between the point of greatest obstruction and the bladder orifice show a somewhat lesser amount of lymph channel proliferation. Here also there was chronic inflammatory infiltration of mucosa, including numerous eosinophils. The kidney showed marked parenchymatous degeneration of tubular epithelium. There also were some small areas of interstitial chronic cellular infiltration. Diagnosis: cavernous lymphangioma of ureter" (fig. 3).

#### DISCUSSION

Lymphangiomas are benign new growths composed of lymph vessels with a supporting connective tissue. They are usually classified as simple, cavernous, or cystic depending on the size of the vessels, whether or not they anastomose, and the presence of cysts. Most are of the cavernous type and this report illustrates one of this type. The vessels are filled with lymph which may be solidified. Blood may be mixed with the lymph. The connective tissue varies in cellularity. Foci of round cells, smooth muscle, and areas of lipoma are sometimes present. Opinion varies as to their origin. Some feel that they form as the result of stasis and are either congenital or acquired. Others feel that they are true neoplasms developing from congenital nests or from connective tissue having the power to form lymph channels.

These tumors are slow growing and may be single or multiple. They originate most commonly in the skin and subcutaneous tissue. They are also found in the muscles and deep areolar tissue of the lip, tongue, neck, axillary region, mediastinum, mesentery, and retroperitoneal regions. Watson and McCarthy, in a report on 1056 blood and lymph vessel tumors, found 41 lymphangiomas; none was intra-abdominal. They considered these tumors to be radioresistant.

A lymphangioma of the kidney has been reported by D. Wynn-Williams. He mentions three previously reported lymphangiomas of the kidney. Reports of twelve other abdominal lymphangiomas have been found. These have been located in the retroperitoneal space and in the mesentery. Mr. E. W. Riches in a report on 2,314 new growths of the kidney and ureter found no similar lesion. He states that the Museum of the Royal College of Surgeons contains none.

Differential diagnosis suggested a primary neoplasm of the ureter. It was obviously not a papillary lesion growing within the lumen of the ureter, but rather an infiltrating lesion of the wall of the ureter. Of all benign ureteral tumors, hemangiomas are most likely to spread in this manner. This might be of help in diagnosis in a patient with a tumor of the ureter, where such a lesion could be suspected from the history of a long duration.

The only curative treatment for a lymphangioma of the ureter is surgical excision. This case illustrates how difficult it would be to do a local excision and



an end-to-end anastomosis. A distinct nodule was felt in the ureter which was thought to be the entire tumor. Lymph vessel formation was found in the ureter from the tumor nodule down to the ureteral orifice, a distance of six centimeters.

The proper choice of incision to expose the lower end of the ureter is important. The ordinary muscle splitting incision gives an opening that is too high and too narrow for anything more than removal of a stone. A midline suprapubic incision is better, and a transverse curved incision is still better. The incision can be shifted a little to the side on which one wishes to expose the ureter.

#### CONCLUSION

A lymphangioma of the ureter is reported.

*622 Eastman Bldg., Boise, Idaho*

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## RE-IMPLANTATION OF URETERS INTO BOWEL FOLLOWING CUTANEOUS URETEROSTOMY FOR DISRUPTION OF URETEROSIGMOIDOSTOMY

CARL K. PEARLMAN

*From the Department of Surgery (Urology), School of Medicine, College of  
Medical Evangelists, Los Angeles, Calif.*

The first case of satisfactory ureterosigmoidal anastomosis following cutaneous ureterostomy was reported in the literature by Dreiling and Hyman. Their patient was treated for carcinoma of the bladder by total cystectomy, total hysterectomy, and cutaneous ureterostomy; later, a ureterosigmoidal implantation was done. The following year Beisler reported two additional cases.

The procedure to be reported here differs from the preceding three in that the sequence of events was ureterosigmoidostomy, disruption of the anastomosis necessitating transplantation of the ureters to the abdominal wall, and finally re-implantation of the ureters into the bowel.

Despite the recorded instances of patients with cutaneous ureteral stoma who have pursued active lives for as long as 25 years, the disadvantages of cutaneous ureterostomy are many: The urinous odor often leads to the patient's feeling unacceptable socially, the cumbersome apparatus for collection of urine and the need for its frequent cleansing. Moreover, a truly satisfactory method of attaching ureterostomy cups to the skin has not yet been devised; consequently the surrounding skin becomes excoriated, inflamed and infected. The ureteral orifices tend to become constricted and may require frequent dilatation; some may even become retracted beneath the cutaneous surface. If ureteral catheters must be employed, it is virtually impossible to prevent ureteritis and pyelonephritis. In the presence of urea-splitting organisms, incrustation is a troublesome complication, although hyaluronidase may be helpful. Ureterosigmoidostomy, on the other hand, often is compatible with a fairly normal life. The latter, where possible, is the procedure of choice.

The patients who would benefit most from ureterosigmoidostomy are those with carcinoma of the bladder; unfortunately they generally constitute poor risks for this procedure. In the past decade the use of blood, protein concentrates, vitamins, the newer sulfonamides and the antibiotics has enhanced the correction of debilitated states to a point where extensive surgical therapy may be undertaken. Emergent diversion of the urinary stream in a critically ill patient, however, oftentimes requires resort to cutaneous implantation of the ureters. It may, in such instances, be a life-saving measure, but consideration of subsequent transplantation of the ureters from the abdominal wall to the bowel may be desirable. Much has been written on uretero-intestinal anastomosis, but the feasibility of re-implanting the ureters into the bowel after cutaneous ureterostomy is not mentioned even in the textbooks. Ureterocutaneous anastomosis generally has been looked upon as an irreversible procedure.

Hazards to intestinal re-implantation of the ureters following cutaneous ure-

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 21, 1952.

terostomy include the difficulty of preserving the ureteral blood supply and the handicap presented by shortening of the ureters as a result of their anastomosis to the abdominal wall. Pyelonephritis and ureteritis interfere with healing of the anastomosis leading to dissolution of the wound and to urinary and fecal fistulas.

Ureters of normal size or with minimal dilatation were, until recently, considered essential to successful implantation by the Coffey technique. However, the introduction of the direct mucosa to mucosa technique has made feasible the transplantation of dilated ureters. The control of infection by the antibiotics and the sulfonamides furthers healing by primary union. Supportive therapy, as previously mentioned, plays an important role. The employment of gastric suction or the Miller-Abbott tube keeps the intestines at rest, thereby protecting the anastomosis.

#### CASE REPORT

J. F., a 44 year old man, when first seen at the Orange County Hospital, had had intermittent bloody urination of 2 years' duration. About one year after the onset of hematuria carcinoma of the bladder had been diagnosed and treated elsewhere by electrofulguration. The bleeding recurred August 1949. On cystoscopic examination a papillary tumor was seen on the right side of the bladder; this extended to the trigone and the vesical neck. The tumor was resected transurethrally and its base fulgurated. The pathologic diagnosis was papillary carcinoma with invasion of the wall of the bladder. In February 1950, small recurrent papillary tumors proximal to and around the right ureteral orifice were destroyed by electrofulguration. He was symptom-free until June 1950, when he again passed bloody urine and clots. Recurrent tumors were seen on the right side of the fundus and also a sessile growth which obscured the right half of the trigone and the right ureteral orifice.

The hopelessness of controlling this neoplasm by electrosurgical means was apparent. Because of his comparatively young age, total cystectomy was thought to offer this patient the best prognosis. Excretory urograms demonstrated an essentially normal renal architecture with good function and a slight dilatation of the right pelvic ureter. A roentgenogram of the chest was normal.

At exploration there were no metastases to the regional lymph nodes or to other organs. Therefore a one-stage cystectomy, prostatectomy, seminal vesiculectomy, and bilateral ureterosigmoidostomy were done. The Coffey No. 1 technique of uretero-intestinal anastomosis was employed. There was, histologically, definite infiltration of the vesical wall by large compact elements of transitional epithelium, the papillary character of which was only suggested. In some of the islands there was loss of membrane with infiltration into the contiguous stroma. Malignancy of the prostate or of the seminal vesicles was not histologically evident.

The patient's postoperative course was stormy and, on the seventh postoperative day, complicated by ileus and bronchopneumonia. Seventeen days after the operation, July 13, urine and feces appeared from the draining sinus into the pelvis. His blood nonprotein nitrogen, which had risen to 78 mg. per hundred cubic centimeters, dropped to 47 mg. On July 19 he had a secondary hemorrhage

which was thought to be controlled by packing, but two days later the hemorrhage became profuse and the patient went into shock. He was given blood.

When the patient's condition improved, the wound was reopened and approximately a quart of blood clots were removed from the pelvis. Ligation of a spurting vessel on the lateral pelvic wall controlled the hemorrhage. The right ureter had become partially separated from the sigmoid and was transplanted to the abdominal wall. The left ureterosigmoid anastomosis was not identified at this time and, because of the patient's critical condition, the wound was closed. He improved rapidly, although he did not pass any discernible urine from the rectum. The absence of left renal function was confirmed by excretory urography August 27. A stricture at the site of the ureterosigmoidal anastomosis was suspected. The abdomen was opened again August 31. The left ureter was markedly dilated, indicating a block at its entrance into the bowel; therefore this ureter also was



FIG. 1. A, retrograde pyelogram through cutaneous stomas. B, photograph of patient 6 months after last re-implantation.

transplanted to the abdominal wall. Although the patient's general condition became considerably improved, an abscess developed in the original incision, extending into the pelvis. This was drained, but an incisional hernia remained. The patient was discharged from the hospital September 21 with catheters in both ureters and with minimal drainage from the pelvis. His nonprotein nitrogen at this time was 43 mg. per hundred cubic centimeters.

Care of the ureteral stomas proved to be unsatisfactory. Ureterostomy cups were discarded because of leakage. Resort to indwelling catheters connected by a Y tube to a rubber urinal attached to the leg was followed by the development of chronic bilateral pyelonephritis and ureteritis.

At this point we were willing to let well enough alone, but the patient insisted on an attempt at re-implantation of the ureters into the bowel. He said he preferred not to live rather than to exist in his unhappy and distressing state. Because of the patient's wish and in the hope that employment of improved anastomotic technique and improved methods of combating infection and promoting early healing, it was decided, 9 months after his discharge from the hospital, to attempt re-implantation of the ureters into the bowel.

Renal function studies, including excretory and retrograde pyelography, were carried out. There was bilateral blunting of calyces with less function on the left side (fig. 1, A). On June 6, 1951, the patient again was operated on. The left ureter was mobilized and the end freshened; it had become dilated to the size of the index finger. The adjacent portion of the sigmoid was extraperitonealized and the ureter was implanted therein by a direct mucosa to mucosa technique. Postoperatively, minimal urinary and fecal drainage from the wound ceased spontaneously. Excretory pyelograms on July 12, 1951, demonstrated the kidney to be functioning, and the patient went home.

He came back to the hospital September 6, for re-implantation of the right ureter. Re-admission had been delayed because of an upper respiratory infection. The operation on the right ureter was done September 13. It was more difficult than that on the left side because it had to be done entirely intraperitoneally. The intestines were matted down and had to be separated before the sigmoid could be approached. The ureter was implanted into the sigmoid by the direct mucosa to mucosa technique. The incisional hernia was repaired at the same time. The postoperative course was uneventful and the patient went home seventeen days after the operation.

He made a good recovery, gaining 30 pounds in weight, and he resumed his work as a welder. Six months later he had an acute exacerbation of the pyelonephritis; this responded promptly to aureomycin. At that time his blood non-protein nitrogen was 63.4 mg. per hundred cubic centimeters and his blood chlorides 566 mg. Excretory urograms revealed some dye in both kidneys. Figure 1, B is a photograph of the patient which was taken 6 months after the last ureterosigmoidal re-implantation. The patient was active and working 1½ years after his last surgery.

The prognosis in this patient will depend on the progression or regression of the pyelonephritis. This would hold true regardless of types of ureterostomy, whether cutaneous or intestinal. Ureteral reflux from the bowel when the direct mucosa to mucosa technique is employed has been demonstrated by several investigators. It may occur in this patient. Whether more damage would be caused by reflux than by the constant passage of catheters into the cutaneous stomas is debatable. The fact that the patient is much happier and more content without external urinary openings would seem to justify the choice of procedure employed.

#### SUMMARY

A case of successful re-implantation of the ureters into the bowel is reported.

The concept that cutaneous ureterostomy is an irreversible procedure should be modified in view of the introduction of improved technique of anastomosis and the availability of antibiotics and chemotherapeutic agents to inhibit infection and thereby promote healing by primary union.

*1511 North Broadway, Santa Ana, Calif.*

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## LEAKAGE AND REFLUX IN URETERO-INTESTINAL ANASTOMOSIS: I. THE FREE PERITONEAL GRAFT

FRANK HINMAN, JR.

*From the Department of Surgery-Urology, University of California School of Medicine,  
San Francisco, Calif.*

The two hazards of direct uretero-intestinal anastomosis are leakage and reflux. Occasional instances of leakage made us try the free peritoneal graft as reinforcement for the anastomosis. Reflux will be considered in a later communication.<sup>1</sup>

Leakage is theoretically more likely after direct anastomosis than in the tunnelled type, such as the Coffey 1. A single row of sutures has been depended on at the juncture of bowel submucosa with ureteral wall, no deep fixation sutures hold the ureteral tip, and a layer of muscle is not used to cover the anastomosis. Freedom from stenosis of the direct transplant, because no free tip can become necrotic and contracted nor a tunnel constrict by a tight suture or scar from infection, has been an advantage outweighing the disadvantage of easier leakage. Rather than abandon the sound principles of the direct anastomosis, we have sought methods of avoiding its complications.

Several means can be used to decrease the chance of leakage. A flap of posterior parietal peritoneum can be brought over the anastomotic site (Nédélec<sup>2</sup>) although this may be impossible to approximate accurately. A tunnel may be formed so that the anastomosis and the ureter proximal to it may be covered.<sup>3, 4</sup> A second row of sutures, either to the surface of the bowel (Cordonnier<sup>5</sup>) or through the muscular coats and serosa (our clinical methods discussed below) offers protection. And last, a free graft of parietal peritoneum may be applied directly over the site of implantation. It is this idea that we have explored in this particular series of experiments.

### THE GRAFT OF PERITONEUM

Following hints of Sano<sup>6</sup> and of Young and Favata<sup>7, 8, 9</sup> on the "sticking on" of skin grafts with plasma and leukocyte cream or thrombin and of Cannady<sup>10</sup> and Mair<sup>11</sup> on the use of skin patches in hernia repair, Devine<sup>12</sup> in 1946 experimentally showed that skin or peritoneum if firmly applied would effectively seal a technically inadequate end-to-end anastomosis of the colon in dogs. Chester,

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 21, 1952.

Supported by the Breon Fund for Medical Research.

<sup>1</sup> Hinman, F. Jr.: Leakage and reflux in uretero-intestinal anastomosis: II, the sub-muscular tunnel. (To be published.)

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<sup>5</sup> Cordonnier, J. J.: Surg., Gynec. & Obst., 88: 441-446, 1949.

<sup>6</sup> Sano, M. E.: Surg., Gynec. & Obst., 77: 510-513, 1943.

<sup>7</sup> Young, F.: Surgery, 15: 450-462, 1944.

<sup>8</sup> Young, F. and Favata, B. V.: War Med., 6: 80-84, 1944.

<sup>9</sup> Young, F. and Favata, B. V.: Surgery, 15: 378-386, 1944.

<sup>10</sup> Cannady, J. E.: Am. J. Surg., 59: 409-419, 1943.

<sup>11</sup> Mair, G. B.: Brit. J. Surg., 32: 381-385, 1945.

<sup>12</sup> Devine, J.: Surg., Gynec. & Obst., 82: 475-479, 1946.

Bell, and McCorkle<sup>13</sup> at this laboratory confirmed Devine's observations by finding that the peritoneal grafts remained viable and adherent. Moore and Singleton<sup>14</sup> were able effectively to seal large defects such as the open duodenal stump and those in the thoracic esophagus and stomach. It occurred to us that such a technic could be effective in ureterosigmoidostomy.

Although the square patch of peritoneum has been fastened with thrombin and plasma adhesive by most workers, Moore and Singleton obtained effective closure with interrupted fixation sutures alone. Since the simpler method would be best for operating room use, we have studied the sutured graft almost to the exclusion of that secured with thrombin-plasma adhesive.

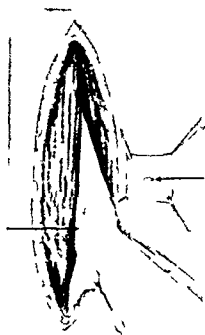


FIG. 1. 2 cm. square graft of peritoneum (and posterior rectus sheath)

#### METHODS AND MATERIALS

The technique, as shown in the accompanying illustration (figs. 1 and 2), requires excision of a 2 by 2 cm. square of parietal peritoneum with or without fascia from the edge of the vertical wound (A). This is perforated at the center and threaded over the stay suture such that the peritoneal surface is toward the ureteral tip. After completion of the direct anastomosis (Hinman, Jr. and Hinman, 1950<sup>15, 16</sup>), the flap is drawn down to cover the suture line and is tacked in place with interrupted cotton sutures (B). Alternatively, the flap is merely held in position until slight adherence is attained, or thrombin-plasma cement is used.

Twenty-two anastomoses were done on 11 mongrel dogs by these variations in method. Forty-two anastomoses without grafts (22 dogs) reported previously were used as controls.

#### RESULTS

The experiments were divided into the following groups: A) thin peritoneal graft without fixation by suture; B) same with fixation; C) full-thickness graft

<sup>13</sup> Chester, S. T., Bell, H. G. and McCorkle, H. J.: *Surg., Gynec. & Obst.*, **89**: 605-608, 1949.

<sup>14</sup> Moore, R. M. and Singleton, A. O. Jr.: *Surg., Gynec. & Obst.*, **92**: 466-468, 1951.

<sup>15</sup> Hinman, F. Jr. and Hinman, F.: *J. Urol.*, **64**: 457-463, 1950.

<sup>16</sup> Hinman, F. Jr.: *J. Urol.*, **64**: 567-571, 1950.

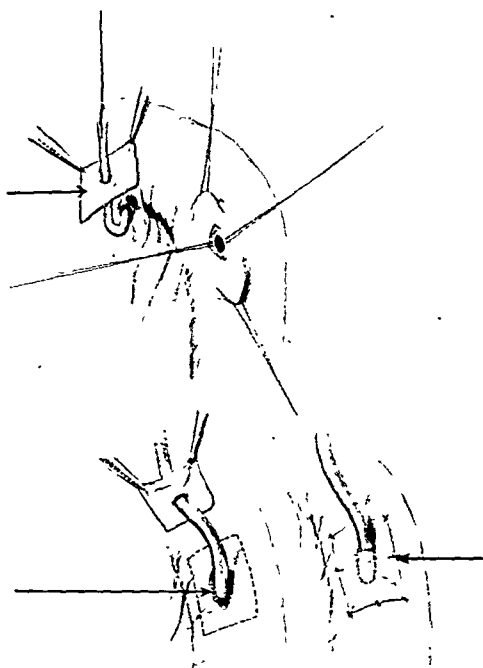


FIG. 2. Graft is sutured over mucosa-to-mucosa anastomosis

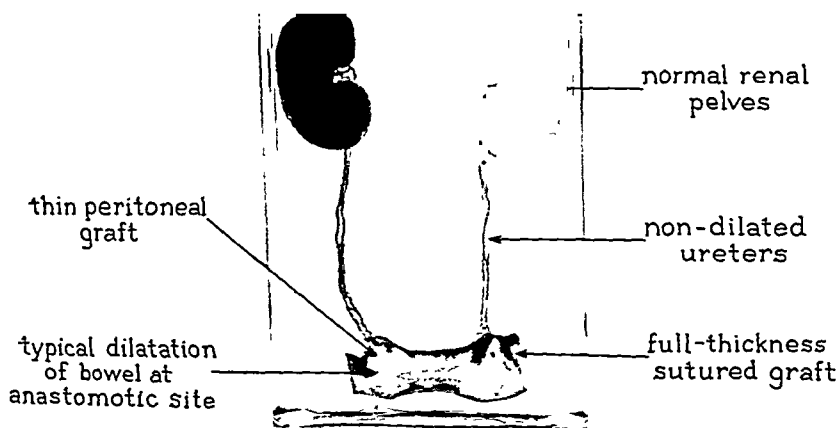


FIG. 3. Thin peritoneal graft on left. Full-thickness graft on right. (Dog. No. 131, 4 months, cleared specimens).

with fixation; D) graft with thrombin-plasma adhesive; E) control series; F) clinical series for comparison.

A) *Thin peritoneal graft without suture fixation* (fig. 2, left). The thin graft was



obtained by excising a square of peritoneum below the linea semicircularis. Here in the dog the peritoneum is filmy in contrast to that taken above that line which would include the fascia of the posterior rectus sheath (full-thickness graft).

This method was least efficient, with three instances of leakage (animal No. 115 L, 105 R and L) and one of severe renal infection (animal No. 56 L) out of 8 anastomoses. The difficulties were movement of the graft and necrosis under and about the non-viable disturbed portion. The graft apparently must maintain close adherence to the ureter and bowel to avoid underlying infection.

*B) Thin peritoneal graft with fixation by suture.* Fixation increased the effectiveness of the graft but was less adequate than the full-thickness with fixation (C), with one instance of leakage (animal No. 123 L) and one of severe renal infection (animal No. 15 L) among 5 anastomoses. Technical difficulties with the delicate graft, noted by others, prevented accurate opposition. Peritoneal patches in the human patient would not need posterior sheath for sufficient body.

*C) Full-thickness graft with fixation* (fig. 3, right). This method was best of all, since obtaining the graft was technically simpler and securing the graft to the site was made easy by its substantial nature. Of 7 anastomoses, none showed leakage and only 2 of the kidneys showed cortical abscesses (animal No. 71 L, 69 L).

*D) Graft with thrombin.* This technique was employed in only 2 grafts because of the obvious difficulties in making it clinically attractive (lack of availability and necessity for preparation of thrombin solution and human plasma for only occasional use). Both grafts showed firm adhesion without serious reaction (animals No. 15 R and 59 R).

Examination of the fixed specimens in series A to D indicated that success was accompanied by minimal reaction beneath the graft (figs. 4 and 5) while failure (leakage or obstruction) resulted from abscess formation in the contaminated closed space beneath the flap. If healing of the abscess occurred, obstruction from fibrosis might follow. Here lies the inherent disadvantage of this method of reinforcement.

*E) Control series.* Comparison with an experimental control series of 28 mucosa-to-mucosa transplants,<sup>14, 15</sup> in which leakage occurred in 2, mild obstruction was found in 4 and severe infection in 4, reveals no statistical advantage of the reinforced anastomosis over the simple mucosa-to-mucosa method.

*F) Clinical series for comparison.* As an alternative to the peritoneal graft, we have added a second row of sutures to our oblique mucosa-to-mucosa anastomosis. Four or five interrupted sutures approximate the loose serosa of the ureter to the serosa and muscularis of the bowel, effectively covering and sealing the deep row of interrupted sutures. Since adoption of this technique (mid-1950), we have had only one instance of leakage.

Animal experiments are being completed and clinical trial made of a tunnel formed with transverse incisions combining some of the advantages of the direct anastomosis with the security against leakage of the graft and the diminution of reflux of the tunnel.

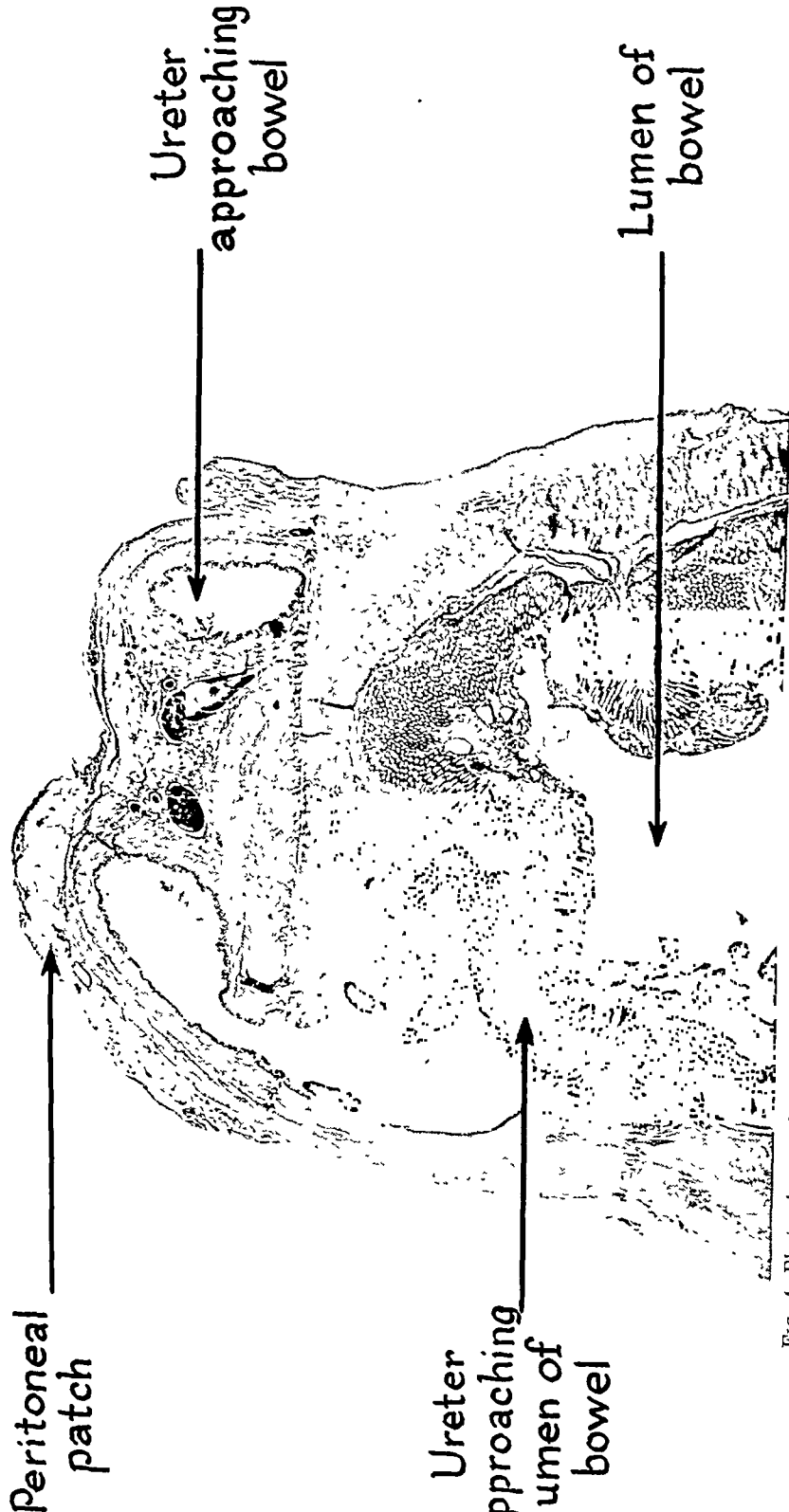


FIG. 4. Photomicrograph, cross-section at site of transplant with full-thickness graft (Dog. No. 196, 2 weeks.)

Peritoneal  
patch

Ureter

Sutures

Wall of  
bowel

Lumen of  
bowel

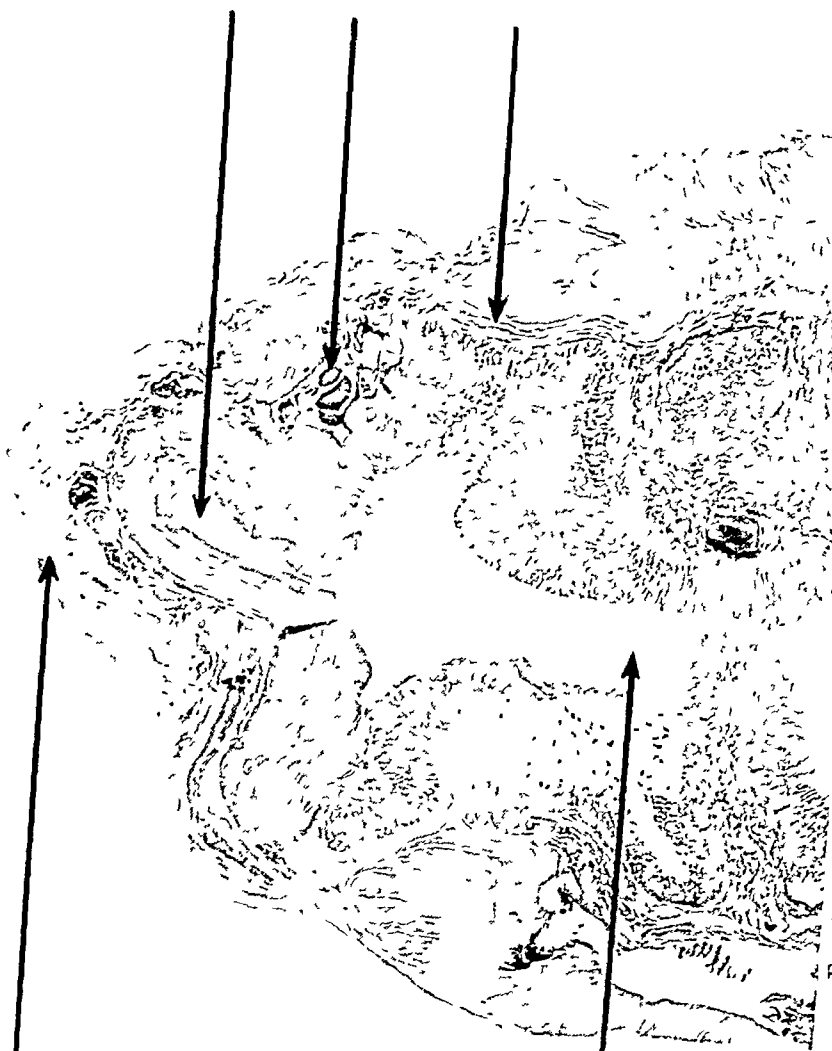


Fig 5 Photomicrograph, full-thickness graft (Dog. No. 69, 2 months)

## DISCUSSION

As we shall discuss in a later paper, assurance against leakage is not enough; but rather, in addition, the need is for prevention of reflux, as by methods of Leadbetter<sup>3</sup> and Weyrauch.<sup>4</sup> A peritoneal graft, while theoretically advantageous, is not significantly superior in experimental anastomosis, nor better than a serosa-serosa reinforcement in our clinical experience. We would reserve the free graft for cases in which an insecure anastomosis could not be reinforced by sutures or effectively implanted in a tunnel.

## SUMMARY AND CONCLUSIONS

A free graft of peritoneum applied at the site of uretero-intestinal anastomosis is technically practical.

Fixation of the graft by sutures is best, although the more inconvenient thrombin-plasma adhesive is effective.

Results of transplantation with a full-thickness graft (peritoneum with posterior rectus sheath) are slightly superior to those without any reinforcement.

However, use of the free peritoneal graft will be limited to the anastomosis with an insecure suture line which cannot be reinforced by an additional row of sutures or by formation of a tunnel.

*University of California Hospital*

## EXPERIMENTAL URETERAL TRANSPLANTS TO AN ILEAL SEGMENT ANASTOMOSED TO THE RECTUM

LEANDER W. RIBA, CHUNGKUNG TSAI AND WALTER G. MADDOCK

*From the Department of Surgery of Northwestern Medical School, Chicago, Ill.*

Since 1851, when Simon<sup>1</sup> described a method for making fistulas between the ureters and the rectosigmoid, numerous techniques have been described for diverting the urinary stream from the bladder into the bowel. A uretero-intestinal anastomosis, however, is an unphysiological procedure since the normally sterile urinary tract becomes infected, with resulting impairment of function and often destruction of the kidneys. In recent years infection has been controlled in part by chemotherapy, antibiotics and improvement in operative technique, but the potential hazards are such that the operation is recommended only when clearly indicated.

The object of this study was to try to minimize the infectious element by anastomosing the ureters to a segment of ileum attached to the rectum in the manner of a long blind diverticulum away from the direct path of the fecal stream (fig. 1). It was thought that peristalsis might materially lessen the entrance of fecal material into the ileal segment, with a consequent lower bacterial count at the site of the uretero-intestinal anastomosis, and also that the downward flow of urine might impede ascending infection.

The idea is not new since a method for diverting the urine into a transplanted small bowel segment was first described in 1907 by Berg,<sup>2</sup> who reported 5 patients operated upon with an immediate mortality of 60 per cent. Other methods of using diverticular segments of the colon have been described,<sup>3-10</sup> but none gave encouraging clinical results.

### METHOD

Healthy dogs were selected and fed on the regular kennel ration. The day before the operation, 15 cc of castor oil was given to clear out the bowel. The operations were carried out under morphine and nembutal anesthesia. Through a lower midline abdominal incision, a small segment of the ileum, varying from

This study was aided by a grant from the Abbott Laboratories.

Accepted for publication October 10, 1952.

<sup>1</sup> Simon, J.: Ectopia vesica; operation for temporary success; autopsy, *Lancet*. 2: 568, 1852.

<sup>2</sup> Berg, J.: The treatment of ectopia vesica. *Surg. Gynec. & Obst.*, 5: 461, 1907.

<sup>3</sup> Van Hook, W.: The surgery of the ureters: A clinical, literary and experimental research. *J.A.M.A.*, 21: 911, 1904.

<sup>4</sup> Peterson, R.: Anastomosis of the ureters with the intestine. A historical and experimental research. *Am. J. Obst.*, 42: 95, 1900.

<sup>5</sup> Hinman, F. et al: An experimental study of uretero-intestinal implantation. The significance of the normal uretero-cloacal arrangement in some reptiles and all aves. *Surg. Gynec. & Obst.*, 69: 713, 1939.

<sup>6</sup> Howard, H. H.: Transplantation of ureter. *J. Urol.*, 61: 735, 1949.

<sup>7</sup> Marshall, V. F. and Gardner, J. S.: An evaluation of the Coffey I method for uretero-intestinal anastomosis. *Surg. Gynec. & Obst.*, 81: 559, 1945.

<sup>8</sup> Jacobs, A.: Transplantation of ureter. *J. Urol.*, 61: 517, 1950.

<sup>9</sup> Cordonnier, J. J.: Uretersigmoid anastomosis. *Surg. Gynec. & Obst.*, 88: 441, 1949.

<sup>10</sup> Higgins, C. C.: Transplantation of the ureters into the rectosigmoid and cystectomy. *Surg. Clin. North Amer.*, p. 1209 (Oct.) 1948.

8 to 20 cm. in length with its attached mesentery, was divided about 9 cm. above the ileocecal junction. Continuity of the ileum was re-established by an end-to-end anastomosis using a two-layer suturing technique of 3-0 chromic catgut for the mucosa and 5-0 black silk for the seromuscular coats. The opening in the mesentery was repaired. The proximal end of the ileal segment was closed with catgut and silk, and the distal end united to the low rectum by an end-to-side anastomosis using one layer of 5-0 black silk interrupted sutures. The abdominal wound was closed with chromic catgut for the peritoneum and interrupted fine silk for the other layers. In 2 dogs the ureters were also anastomosed to the ileal

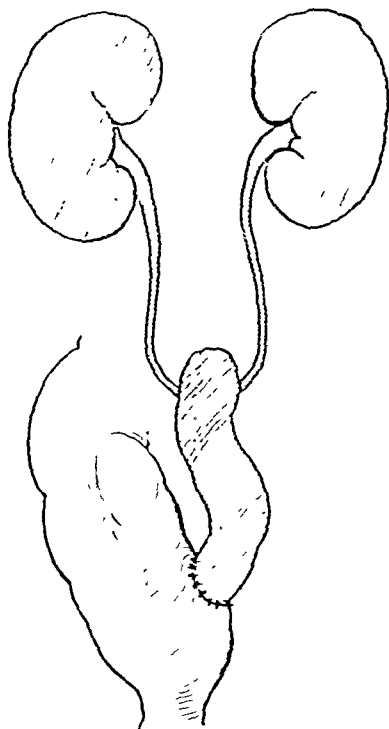


FIG. 1. Diagram of ureters anastomosed to ileal segment attached to low rectum.

segment at this first operation, but this one-stage procedure was abandoned because of the high mortality and uretero-ileal segment anastomosis was carried out as described in the following paragraphs.

About 2 to 3 weeks later, the second stage was done through a right lower quadrant midrectus incision. The right ureter was transplanted to the upper end of the ileal segment in the following manner. It was handled gently, with minimal trauma and the avoidance of any angulation, torsion, tension, or compression in order not to interfere with its blood supply. The ureter was exposed as little as possible, not stripped of its perivascular blood supply, and carefully divided about 2 cm. above the urinary bladder. The distal end was tied with silk. Following the method of Nesbit, the proximal end was split longitudinally for

TABLE 1 *Summary of data*

## Group 1 One stage operation

Isolation of the ileal segment and its anastomosis to the rectum, immediately followed by bilateral ureteral transplants to the ileal segment

| DOG NO | LENGTH ILEAL SEGMENT | POSTOPERATIVE COURSE        | PATHOLOGY                                                                  |
|--------|----------------------|-----------------------------|----------------------------------------------------------------------------|
| 1      | 8 cm                 | Died in 46 hours            | Peritonitis due to leakage at uretero ileal anastomosis                    |
| 2      | 10 cm                | Died 7 days postoperatively | Bilateral pyonephrosis Dilatation of ureters with stricture at anastomosis |

## Group II Two stage operation

Stage 1 Ileal segment developed and anastomosed to the rectum

Stage 2 Bilateral uretero ileal segment anastomosis

| DOG NO | LENGTH ILEAL SEGMENT | POSTOPERATIVE COURSE                                                           | PATHOLOGY                                                                                                       |
|--------|----------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| 3      | 20 cm                | Died 10 days after 2nd stage                                                   | Gross appearance<br>Bilateral pyonephrosis<br>Microscopic<br>Acute pyelonephritis                               |
| 4      | 15 cm                | Died 28 days after 2nd stage                                                   | Gross appearance<br>Bilateral hydronephrosis and hydroureteritis<br>Microscopic<br>Acute pyelonephritis         |
| 5      | 18 cm                | Died 26 days after 2nd stage                                                   | Gross appearance<br>Bilateral pyoureteritis and pyonephrosis<br>Microscopic<br>Acute suppurative pyelonephritis |
| 6      | 20 cm                | Died 24 hours after 1st stage                                                  | Strangulation of the transplanted ileal segment                                                                 |
| 7      | 15 cm                | Living and well for 138 days, then sacrificed                                  | Gross<br>Slight dilatation of both kidneys and ureters<br>Microscopic<br>Chronic pyelonephritis                 |
| 8      | 20 cm                | Died 21 days after 2nd stage                                                   | Gross<br>Slight dilatation of both kidneys and ureters<br>Microscopic<br>Chronic pyelonephritis                 |
| 9      | 25 cm                | Died 18 hours after 1st stage                                                  | Peritonitis due to leakage from the ileo rectal anastomosis                                                     |
| 10     | 20 cm                | Blood NPN 107.5 mg % 10 days after 2nd stage<br>Died 20 days later from uremia | Gross<br>Slight dilatation of kidneys and ureters<br>Microscopic<br>Ac & Chr pyelonephritis                     |

TABLE 1. *Continued*Group II—*Continued*

| DOG NO. | LENGTH ILEAL SEGMENT | POST-OPERATIVE COURSE                                                           | PATHOLOGY                                                                                                            |
|---------|----------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| 11      | 18 cm.               | Blood NPN 350 mg. % 10 days after 2nd stage. Died 17 days later from uremia.    | Gross:<br>Slight pyonephrosis with moderate dilatation of the ureters<br>Microscopic:<br>Ac. & chr. pyelonephritis   |
| 12      | 16 cm.               | Blood NPN 54.5 mg. % 10 days after 2nd stage. Died 53 days later from pneumonia | Gross:<br>Right lobar pneumonia. Slight dilatation of kidneys and ureters<br>Microscopic:<br>Moderate pyelonephritis |

## Group III. Three-stage operation.

Stage 1. Ileal segment developed and anastomosed to the rectum.

Stage 2. Right ureter anastomosed to ileal segment.

Stage 3. Left ureter anastomosed to ileal segment.

| DOG NO. | LENGTH ILEAL SEGMENT | POSTOPERATIVE COURSE                                                                  |                                                                                                                   | PATHOLOGY                                                                                                                                                |
|---------|----------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
|         |                      | Blood NPN mg. %                                                                       | Bacteriology Cultures                                                                                             |                                                                                                                                                          |
| 13      | 14 cm.               | 63.2—15 days after 2nd stage; 34.2—21 days after 3rd stage                            | Rt. ureter:<br>Proteus +<br>E. coli +<br>Ileal segment:<br>Proteus +++<br>E. coli +++<br>Lt. ureter:<br>No growth | Died 3 months after 3rd stage<br>Gross:<br>Normal kidneys; slight dilatation of ureters<br>Microscopic:<br>Chr. mild pyelonephritis                      |
| 14      | 14 cm.               | 20.4—7 days after 1st stage; 34.2—10 days after 2nd stage; 177—7 days after 3rd stage | Rt. ureter & ileal segment content:<br>Proteus +++<br>E. coli +++<br>Lt. ureter:<br>No growth                     | Died 27 days after 3rd stage from uremia<br>Gross:<br>Marked bilateral pyonephrosis & dilatation of ureters<br>Microscopic:<br>Ac. & chr. pyelonephritis |
| 15      | 14 cm.               | 500.—10 days after 2nd stage                                                          | Rt. ureter & ileal segment content:<br>Proteus +++<br>E. coli +++<br>Lt. ureter:<br>No growth                     | Died 2 days after 3rd stage from peritonitis, bilateral pyonephrosis and dilatation of ureters; peritonitis from leakage at lt. ureteral transplant      |



TABLE 1. *Continued*Group III *concluded*

| DOG NO. | LENGTH ILEAL SEGMENT | POSTOPERATIVE COURSE                                     |                                                                                                                       | PATHOLOGY                                                                                                                                                                     |
|---------|----------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         |                      | Blood NPN mg %                                           | Bacteriology Cultures                                                                                                 |                                                                                                                                                                               |
| 16      | 12 cm.               | 78.5—10 days after 2nd stage; 170—2 days after 3rd stage | Rt. ureter:<br>Proteus +++<br>E. coli ++<br>Seg. Content:<br>Proteus ++++<br>E. coli ++++<br>Lt. ureter:<br>No growth | Died 3 days after 3rd stage of uremia & peritonitis.<br>Gross:<br>Rupture of left kidney from complete obstruction at left uretero-ileal segment anastomosis                  |
| 17      | 12 cm.               | 100.—10 days after 3rd stage                             | Rt. ureter & ileal segment content:<br>Proteus ++++<br>E. coli ++++<br>Lt. ureter:<br>No growth                       | Died 48 days after 3rd stage of uremia.<br>Gross:<br>Bilateral pyonephrosis and cortical abscess; moderate dilatation of ureters<br>Microscopic:<br>Ac. & chr. pyelonephritis |
| 18      | 12 cm.               | 104.—14 days after 3rd stage                             | Same as 17                                                                                                            | Sacrificed 14 days after 3rd stage<br>Gross:<br>Bilateral and slight dilatation of ureters and kidneys<br>Microscopic:<br>Mild ac. pyelonephritis                             |
| 19      | 10 cm.               | 222.—7 days after 3rd stage                              | Not done                                                                                                              | Sacrificed 5 months after the 3rd stage<br>Gross:<br>Apparent normal kidneys and ureters<br>Microscopic:<br>Mild ac. & chr. pyelonephritis                                    |

The results of the indigocarmine renal function tests on dogs 14 and 17 at the time of the 3rd stage were:

- Dog 14. Right side: No dye 30 minutes after injection.  
Left side: Dye appeared 3 minutes after injection.  
Dog 17. Right side: No dye 30 minutes after injection.  
Left side: Dye appeared 6 minutes after injection.

1.2 cm. producing a spatula shape. A longitudinal incision of about 1.2 cm. was made approximately 2 to 3 cm. from the closed end of the ileal segment and an elliptical anastomosis of the spatula end of the ureter and the intestine was carried out by a careful two-layer technique, uniting mucosa to mucosa and serosa of the bowel to the adventitia of the ureter. The initial suture of 5-0

chromic catgut with an atraumatic needle attached at both ends picked up the proximal angle of both the ureteral and the incised bowel mucosa. The middle of the suture was tied at this point, and each end used to approximate the mucosae of its side with a continuous locked stitch. The outside layer of interrupted 5-0 chromic catgut approximated but did not invert the bowel serosa and ureteral adventitia. By this method a relatively large anastomosis was obtained, which it was hoped would lessen such complications as scar tissue or late stenosis.

The third stage, done 2 to 3 weeks later through a left midrectus incision, consisted of a transplant of the left ureter to the ileal segment in the same manner as the second stage. At this time when the slit was made in the ileal segment for the left ureter transplant, the contents of the segment were observed and specimens of material taken for culture. The right ureteral orifice was observed and carefully catheterized for urine culture and smear. The left ureter, before being anastomosed, was catheterized for urine culture. In two dogs, differential renal function tests were done by injecting indigo carmine intravenously.

Postoperatively for all stages, sulfonamide 1 gram and streptomycin 0.5 gram were given daily for one week. All dogs were kept on a routine general diet.

#### DATA

These are summarized in table 1.

#### DISCUSSION

All dogs were closely observed during the period of their life. The one-stage series (group I) was abandoned because of the high mortality, and multiple stage operations were used thereafter.

The length of the ileal segment was increased in several dogs to 18-25 cm. with the idea that through downward peristalsis it might remain cleaner and the chances of infection from the large bowel thus reduced. However, it was found that most of these animals died of uremia, the blood nonprotein nitrogen rising up to 350 mg. per cent in dog 11. Using ileal lengths of 8, 10, 12, 14, 16, 18 and 20 cm., the severity of the uremia was found to be approximately proportionate to the length of the ileum; i.e., the longer the transplanted ileum, the more severe the uremia. An ileal segment of 12 to 14 cm. was finally adopted because although the blood nonprotein nitrogen rose, the elevation did not seem to be serious.

At the third stage operation of group III, examination of the right ureter showed slight to marked dilatation, and on opening the ileal segment there was edema and some scar tissue narrowing at the uretero-ileal segment anastomosis. No gross fecal material was found in the ileal segment, but always a small amount of clear or mucoid fluid which bacteriological studies showed to be heavily infected with colon group organisms. All urine obtained from the previously transplanted right ureters by careful catheterization through the ileal segment was cloudy and on culture always showed a heavy growth of bacteria. It was apparent that intestinal tract bacteria easily passed up the ureters. To substantiate this upward flow, in dog 10 a radiopaque fluid was injected under

very slight pressure into the ileal segment near its anastomosis with the rectum. X-ray films showed an immediate reflux of this material up to the renal pelvis. There was no sphincter action at the anastomosis.

Urinary tract infection occurred in all of the dogs in this study, anastomosis to the transplanted ileal segment failing to prevent this undesirable complication. This result is in accord with findings on almost all uretero-intestinal transplants on dogs, a few of which are quoted: Morestin<sup>11</sup> in 1893 did 10 bilateral and 14 unilateral transplantations in 24 dogs. All except one died of peritonitis, nephritis, hydronephrosis or infection. Martin<sup>12</sup> in 1899 operated upon 42 dogs with only 5 recoveries. Deaths were due to pyelonephritis, numerous bacteria in the kidneys, and chronic interstitial nephritis. Hinman<sup>13, 14</sup> reported a transplant study performed by 10 different methods on 53 dogs with the results of 11 dying from peritonitis due to leakage at the site of anastomosis; 7 from acute pyelonephritis; 8 from pyonephrosis; 3 from uremia; and the rest being either sacrificed or dying from such other causes as evisceration, pneumonia, etc. Nesbit<sup>15, 16</sup> in 1948 performed the spatula mucosa to mucosa operation upon dogs as well as upon humans. In each dog only one ureter was transplanted. The pyelograms made 1 or 2 months postoperatively disclosed no hydronephrosis and little if any abnormality in the ureters. In 1950 Thompson<sup>17</sup> reported some observations on isolated sigmoid loop substitutions following total cystectomy in 6 dogs: 5 dogs were alive and well from 5 to 11 months following operation with satisfactory renal status; only 1 dog had pyonephrosis of the right kidney. In the early period after operation, some of these dogs showed slight to moderate hydronephrosis and hydro-ureters and some had marked hydronephrosis and impaired renal function, but after 2 months some of them showed a return of normal renal function. Hinman<sup>18</sup> in 1950 reported 42 transplants on 21 dogs by an open submucosal uretero-intestinal anastomosis. One dog died in 18 hours without recovering from the anesthesia; 6 dogs died within the first postoperative week, the cause in 2 cases being peritonitis from a detached ureter, but no cause was determined in the remaining four. The other 14 dogs died or were sacrificed within 10 days to 18 months. An autopsy of 2 of these showed slight ureteral dilatation; another 2 had evidence of renal infection severe enough to explain the death. The remaining 10 were reported to have normal ureters and pelvis and little or no pyelonephritis.

Previous experimental studies by Riba<sup>19</sup> showed 100 per cent postoperative

<sup>11</sup> Morestin, H.: Greffe d'ureters. Bull. Soc. Anat. de Par., 17: 796, 1892.

<sup>12</sup> Martin, F. H.: Implantation of ureters in rectum; a method having for its object the making of subsequent infection of the ureters and kidneys impossible. J.A.M.A., 32: 159, 1899. Implantation of ureters in the bowels. N. Am. Pract., 11: 67, 1899.

<sup>13</sup> Hinman, F.: An experimental study of uretero-intestinal implantation. The cause of peritonitis. Surg. Gynec. & Obst., 62: 909, 1936.

<sup>14</sup> Hinman, F. and Weyrauch, H. M., Jr.: A critical study of the different principles of surgery which have been used in uretero-intestinal implantation. Internat. Abstr. Surg., 64: 313, 1937.

<sup>15</sup> Nesbit, R. M.: Ureterosigmoid anastomosis by direct elliptical connection. Univ. Hosp. Bull., Ann Arbor, 14: 45, 1948.

<sup>16</sup> Nesbit, R. M.: Ureterosigmoid anastomosis. J. Urol., 61: 728, 1949.

<sup>17</sup> Thompson, H. T.: Isolated sigmoid loop substitution following cystectomy in dog. J. Urol., 64: S5, 1950.

<sup>18</sup> Hinman, F. and Hinman F., Jr.: Ureteral implantation. J. Urol., 64: 457, 1950.

<sup>19</sup> Riba, L. W.: Ureteral-intestinal anastomosis. J. Urol., 67: 284, 1952.

pyelonephritis of varying degrees following uretero-intestinal anastomosis. In his dogs, with excellent drainage, urine obtained by a puncture of the ureter above the anastomosis always revealed low-grade infection or a bacilluria.

This paper presents additional laboratory experience in uretero-intestinal anastomoses. The Nesbit spatula type of oblique attachment was found to be simple and practical, but it afforded no especial protection against urinary tract infections or some late contraction at the uretero-intestinal anastomosis. The method of bringing the ureters to a segment of ileum attached to the rectum showed no useful advantage.

#### SUMMARY AND CONCLUSIONS

In an attempt to minimize kidney infection following uretero-intestinal anastomosis, the ureters of dogs were attached to a segment of ileum transplanted to the rectum. It was hoped that the ileal segment, connected as a diverticulum away from the fecal stream, would be freer of infecting fecal material than the rectum itself. The procedure proved to be of no value.

A one-stage operation, anastomosing the ileal segment to the rectum and both ureters to the segment, was abandoned because of the high operative mortality. A two or three-stage procedure was quite satisfactory.

The spatula technique was used for the uretero-intestinal anastomosis. All of the orifices contracted to a slight degree, only a few to a marked extent.

Of the 19 dogs used in the study, two died of peritonitis and two of pneumonia; seven died of known uremia, five more of probable uremia (the blood nonprotein nitrogen was not done). Only three lived and were sacrificed for examination.

Bacteriological studies showed marked urinary tract infection in all of the dogs. Pathological findings were varying degrees of pyonephrosis, hydronephrosis, hydro-ureters, and acute and chronic pyelonephritis.

The dog was considered to be a rather poor animal for this study, since the ureters are small and the intestinal wall is thick and tough.

Uretero-intestinal anastomosis is far from an ideal procedure, but in humans circumstances sometimes force its accomplishment.

*720 N. Michigan Ave., Chicago, Ill.*

## AUTOGENOUS VEIN GRAFTS AND VENOUS VALVES IN URETERAL SURGERY: AN EXPERIMENTAL STUDY

MILTON L. ROSENBERG\* AND GREGORY A. DAHLEN

*From the Department of Surgery, Division of Urology, Stanford University School of Medicine, San Francisco, Calif.*

This report is an experimental study of the use of fresh autogenous vein grafts in ureteral surgery in dogs. The experiment is divided into two parts: part 1 being a study of the application of the venous valvular system in the prevention of fecal or urinary reflux up the ureter in ureterosigmoidostomy or ureterocystoneostomy and part 2 being a study of the use of vein grafts in the repair of ureteral defects.

Free vein grafts have been used experimentally in repairing common bile duct defects and in surgery of the major blood vessels. Veins such as the internal saphenous are simple to obtain in any desired length and circumference and they have a unique valve system that prevents reflux of blood and could theoretically prevent reflux of urine. Blood vessel banks have further increased the availability of veins of all sizes for grafts.

The repair of ureteral defects and the prevention of reflux of urine in ureterosigmoidostomy and ureterocystoneostomy are difficult surgical problems. Ureteral injury or disease commonly leads to nephrectomy or permanent nephrostomy because of insufficient length of patent ureter. In ureterosigmoidostomy, the reflux of feces up the ureter to the kidney has led to serious complications. In addition, ureteral reflux of urine from an infected or obstructed neurogenic bladder or following re-implantation of the ureter into the bladder has often caused serious upper tract damage.

### HISTORICAL METHODS OF URETERAL REPAIR

Many methods for repairing ureteral defects have been advocated. We have been unable to discover previous reports in which vein grafts were used although McClure<sup>1</sup> in 1907 transplanted segments of carotid artery and jugular vein to the ureters of dogs. The results of these studies were not published, but apparently stenosis of the graft with complete obstruction occurred.

*Arterial grafts.*—Calef<sup>2</sup> used a segment of common iliac artery to bridge ureteral defects in dogs. Hydronephrosis and destruction of the kidney occurred even though the artery showed endothelial proliferation which could not be differentiated from ureteral epithelium. The obstruction was believed to be due to interruption of the peristaltic wave.

*Intestinal grafts.*—Small bowel was used by Nissen<sup>3</sup> for a patient with an end-

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 21, 1952.

\* Bank of America-Giannini Foundation Fellow in Urology.

Joseph F. McCarthy prize essay. *Editor*

<sup>1</sup> Personal communication, Dr. Miley B. Wesson.

<sup>2</sup> Calef, C.: *Ann. ital. di chir.* 17: 153-172, 1938 (abstracted in *Ztschr. f. urol. Chir.*, 44: 185, 1938-1939).

<sup>3</sup> Nissen, R.: *J. Internat. Coll. Surg.*, 3: 99-101, 1940.

to-end anastomosis between ureter, bowel and bladder. Longuet<sup>4</sup> used a continuous circular loop of ileum with a side-to-side anastomosis between ureter and bowel with a wide anastomosis between bowel and bladder. Postoperative studies of these cases were not complete. Both of these methods have the disadvantage of pooling of urine with increase in infection and reflux, identical with that in a bladder diverticulum.

*Bladder flaps.*—Bladder flaps rolled as a tube to replace the distal ureter have been used successfully. Boari<sup>5</sup> performed this operation on a dog in 1894, but no follow-up studies were obtained. Demel<sup>6</sup> reported a method in dogs in which two-thirds of the ureter could be replaced by a bladder flap and Baidin<sup>7</sup> used this method successfully in a case of uretero-uterine fistula. Spies and his co-workers<sup>8</sup> and Barnes and Farley<sup>9</sup> advocated modifications of the bladder flap method. These methods have the disadvantages of insufficient length, limited use to the distal third of the ureter and no prevention of reflux.

*Metal tubes.*—Vitalium tubes were used as splints with good results in the ureters of dogs by Lord and Eckel.<sup>10</sup> No calcium deposition occurred so long as the urine remained sterile. However, when vitalium tubes were used in uretero-intestinal anastomosis in dogs by Stevens and Lord,<sup>11</sup> calcification took place in three to four weeks. Lord, Stefko and Stevens<sup>12</sup> found that free fascial grafts from the anterior rectus sheath of the dog placed over a vitalium tube worked well when the urine was sterile. However, free peritoneal and free bladder grafts failed in every experiment because of their tendency to slough. Tantalum tubes were used by Lubash<sup>13</sup> in ureterosigmoidostomy, but the results were not conclusive.

*Dermal grafts.*—Bettman<sup>14</sup> fashioned a subcutaneous skin tube between a cutaneous ureterostomy and the bladder in one patient with apparently good functional results.

#### VEIN GRAFTS IN COMMON BILE DUCT REPAIR

Free vein grafts have been used experimentally for the repair of common bile duct defects in dogs. Shea and Hubay<sup>15</sup> utilized a non-suture technique<sup>16</sup> over Blakemore-Lord vitalium tubes in 21 animals. In 14 of these the bridging venous channels remained patent, maintaining a good flow of bile. Of these 14, a pliable channel lined with biliary epithelium developed in 5 dogs and nine maintained the original vein graft. Four cases were considered failures because of obstruction

<sup>4</sup> Longuet, Yves-Jacques: *Urol. & Cutan. Rev.*, 52: 322-326, 1948.

<sup>5</sup> Boari, A.: *Chirurgia dell' uretere*, con prefazione del Dott. I. Albaran, 1900, 14, 444; Contributo sperimentale alla plastica delle uretere, *Atti della aacad. della scienze med., e naturali di Ferrara*, Seduta 27 maggio, 1894. (Quoted by Spies, Johnson and Wilson.)

<sup>6</sup> Demel, R.: *Zentralbl. f. Chir.*, 51: 2001-2008, 1946.

<sup>7</sup> Baidin, A.: *Zentralbl. f. Gynäk.*, 54: 3237-3239, 1930.

<sup>8</sup> Spies, J. W., Johnson, C. E. and Wilson, C. S.: *Proc. Soc. Exper. Biol. & Med.* 30: 425-426, 1932-1933.

<sup>9</sup> Barnes, R. W. and Farley, S.: *J. Urol.*, 59: 466-470, 1948.

<sup>10</sup> Lord, J. W. and Eckel, J. H.: *J. Urol.*, 48: 412-420, 1942.

<sup>11</sup> Stevens, A. B. and Lord, J. W.: *ibid.*, 50: 574-579, 1943.

<sup>12</sup> Lord, J. W., Stefko, P. L. and Stevens, A. R.: *ibid.*, 49: 249-254, 1943.

<sup>13</sup> Lubash, S.: *ibid.*, 57: 1010-1025, 1947.

<sup>14</sup> Bettman, A. G.: *Plastic & Reconstructive Surgery*, 2: 80-86, 1947.

<sup>15</sup> Shea, P. C. and Hubay, C. A.: *Ann. Surg.*, 128: 21-29, 1948.

<sup>16</sup> Blakemore, A. H. and Lord, J. W.: *Ann. Surg.*, 121: 435-453, 1945.

or necrosis and rupture of the graft and three animals died of distemper. Lord and Chenoweth<sup>17</sup> used venous grafts in the common bile duct of 10 dogs. In six of these epithelialization occurred on the inner surface of the grafts with marked shrinkage of the graft being noted. In four of the animals leakage or sloughing and stricture of the graft occurred. Horsley<sup>18</sup>, 1918, inverted a segment of vein and sutured it into experimentally made canine common duct defects. After a few months the vein contracted and became completely obstructed.

#### VEIN GRAFTS IN ARTERIAL REPAIR

The efficacy of autogenous venous grafts in the repair of arterial defects over vitallium tubes was demonstrated by Blakemore and Lord.<sup>16</sup> Preserved heteroplastic vein grafts were also used successfully by these workers and by Macpherson and his co-workers<sup>19</sup>. It was found that in homografts some of the fibrous and elastic tissue in the middle coat persisted, but that the cellular elements degenerated slowly. The intima was replaced by a fibrocellular layer from the host vessel, the other layers being replaced by reactive ingrowth of fibroblasts from the perivascular tissues within a 3-month period.

Since vein grafts had been used with success in the repair of experimentally made bile duct and vascular defects, their potential use in ureteral surgery appeared feasible. Many obvious anatomical and physiological differences exist between these structures and the fluid contents of each, but the significance of these differences upon the survival of venous autografts in ureters, has been unknown prior to the present study. For example, the pH of bile ranges from 6.9 to 7.7, while the pH of urine is considerably lower. The blood supply to venous grafts in arteries is undoubtedly greater than to grafts in ureters and arterial hydrostatic pressure is greater than the pressure of urine in the normal ureter. In addition, the presence of ureteral peristalsis is important in the normal transport of urine and peristaltic action is absent in the venous segment.

#### VENOUS VALVES

The venous valvular system prevents reflux of blood while assisting the flow of blood to the heart against the influence of gravity. Figure 1 demonstrates the efficacy of the valves in the femoral vein of a dog. A glass cannula was introduced into the femoral vein cephalad to the segment of vein used as a graft. Bismuth oxychloride was injected by manual pressure on a 50 cc Luer syringe so that the vein segment was distended maximally. In every case valvular competency prevented significant retrograde flow of contrast media. Valves, which are composed of a double layer of endothelium with an intervening layer of connective tissue are usually bicuspid, but can be tricuspid. Figure 2 depicts a segment of the femoral vein of a dog identical with that used for grafts in this experiment. The wall of the vein is usually dilated on the cardiac side of a valve into a shallow sinus so that when the vein is distended it assumes a nodulated

<sup>17</sup> Lord, J. W. and Chenoweth, A. I.: *Arch. Surg.*, 46: 245-252, 1943.

<sup>18</sup> Horsley, J. S.: *J.A.M.A.*, 71: 1188-1196, 1918.

<sup>19</sup> Macpherson, A. I. S., Nabatoff, R. A., Deterling, R. A., Jr. and Blakemore, A. H.: *Arch. Surg.*, 63: 152-161, 1951.

appearance. The free border of the valve is lunate, having a deep concavity. In the upper end of the saphenous vein in humans, there are usually two or three pairs of valves within six or seven centimeters.<sup>20</sup> Valves are abundant in the veins of the extremities but are lacking in the superior and inferior vena cavae, hepatic, portal, renal, uterine, pulmonary, umbilical, cerebral and meningeal veins and in the veins of bones.



FIG. 1. Retrograde injection of common femoral vein to demonstrate competency of venous valves.

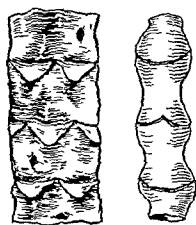


FIG. 2. Valves in segment of femoral vein similar to that used in ureterovenosigmoidostomy.

#### EXPERIMENTAL METHODS AND RESULTS

*General method.*—A total of 12 healthy mongrel dogs, each weighing between ten and twelve kilograms, was used and unilateral free vein grafts were carried out in each animal. Only one ureter was bridged experimentally or transplanted in each animal because we wished to study only the healing and functional result of the vein graft. We therefore did not wish to risk bilateral ureteral obstruction. Nembutal anesthesia was used throughout the experiment. In each case the segment of vein was removed first using no clamps or ligatures on the graft itself. By dissection of 12 femoral veins prior to beginning this study, at least one and usually two or more pairs of valves were found consistently in the vein

<sup>20</sup> Ochsner, A. and Mahorner, H.: *Varicose Veins*, St. Louis: C. V. Mosby Co., 1939, p. 45.



segment used. The cephalad end of the vein segment was tagged with a fine No. 0000 atraumatic chromic suture and the vein was bathed in warm saline until the anastomotic site in the ureter was prepared. The complete study consisted of six ureterovenosigmoidostomies, four ureteroveno-ureterostomies and two ureterovenocystostomies. Each group will be described separately.

*Ureterovenosigmoidostomy.*—Unilateral ureterovenosigmoidostomy was carried out in 6 dogs, three times on the right ureter and three on the left. A femoral vein segment 2 cm. in original length was used and the direction of the vein was reversed so that valvular action would permit the flow of urine into the bowel but would prevent the reflux of feces. The distal end of the ureter was prepared by cutting the ureter transversely with a scalpel at the junction of the middle and lower thirds. Maximal blood supply to the ureter was preserved. The distal third of the ureter ligated with a No. 00 chromic gut suture. The original caudal



FIG. 3, A, barium enema in dog 1 month after right ureterovenosigmoidostomy. No urine reflux occurs. B, excretory urogram 1 month after right ureterovenosigmoidostomy.

end of the vein graft was then sutured to the ureter with four No. 0000 atraumatic chromic gut sutures that penetrated the entire thickness of each wall. The original cephalad end of the vein was sutured to the sigmoid colon by a mucosa-to-mucosa type anastomosis as described by Cordonnier.<sup>21</sup> Absorbable sutures were used throughout this portion of the experiment. No leakage was seen and urine flowed freely through the graft. No drains were used. Preoperative bowel preparation had consisted of nothing by mouth for 24 hours and two tap water enemas.

All six animals remained clinically healthy until they were sacrificed. Stools were liquid in all of the animals immediately following operation and for at least 10 days postoperative. In 2 dogs, the stools gradually became formed after 10 days and were solid after 3 weeks. These animals were sacrificed at 4 and 6 weeks respectively. The four remaining dogs maintained liquid stools until they were sacrificed at 4, 5, 6 and 8 weeks. Excretory urograms and barium sulfate enemas were performed every 2 weeks on all animals. For the pyelograms,

<sup>21</sup> Cordonnier, J. J.: Surg. Gynec. & Obst., 88: 441-446, 1949.

20 ml. of 35 per cent diodrast was given intravenously and films were taken before injection and 5, 10 and 15 minutes after injection. Enemas containing 200 to 400 ml. of barium sulfate suspension were given from a height of 2 feet. Reflux up the ureter did not occur in any case even though excretory urograms revealed patent orifices at the ureterovenosigmoidostomy junction. Figure 3, *A* is an x-ray of a barium enema in a dog having a right ureterovenosigmoidostomy one month after operation. Figure 3, *B* is an excretory urogram in the same animal 1 day before the enema was given. Although the right kidney is mildly hydronephrotic, there is excretion of dye by the kidney with emptying into the



FIG. 4. *A*, left ureterovenosigmoidostomy 4 weeks after operation. *B*, left ureterovenosigmoidostomy 5 weeks after operation.

sigmoid. An excretory urogram of a left ureterovenosigmoidostomy 4 weeks after operation is shown in figure 4, *A*. The vein segment does not fill, but the diodrast enters the bowel. The dog whose pyelograms are seen in figure 4, *A* was sacrificed 5 weeks after operation and figure 4, *B* demonstrates the hydronephrosis and hydro-ureter seen on the pyelogram (formalin-fixed specimen). The vein graft could not be identified grossly and the anastomotic site was a 5 mm. fibrous, thickened cord with a narrow but patent lumen.

At autopsy of each animal a bowel segment, including the anastomotic site, was removed and bismuth suspension was forcibly injected through a Luer syringe at one end. No dye entered the ureter or kidney. The venous segment was shortened to less than half its original length and it was thickened and fibrous in every case. No dense adhesions were found around the graft and there was no other evidence of leakage. A varying degree of hydronephrosis and hydro-ureter was found in every case but no complete obstruction. Cut sections revealed

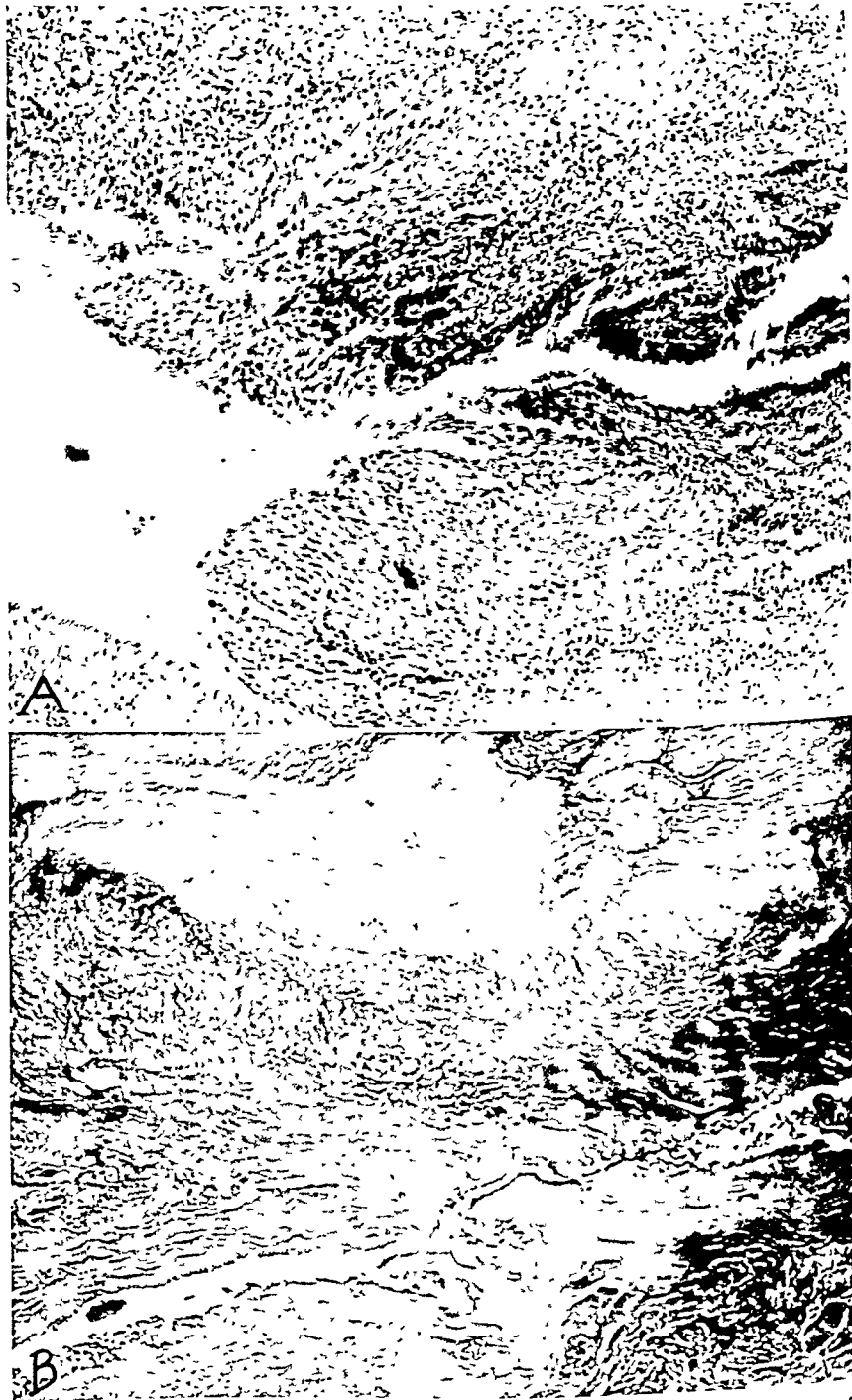


FIG. 5. *A*, photomicrograph (H & E  $\times 100$ ) of ureterovenous junction 6 weeks after ureterovenosigmoidostomy. Transitional epithelium lines autograft and there is fibroblastic invasion of venous wall. *B*, photomicrograph of vein autograft (van Gieson-Weigert  $\times 50$ ) 8 weeks after ureterovenosigmoidostomy. Channel and graft are almost obliterated. Elastic fibers are clumped in lower portion of vein. Fibrous tissue has replaced cellular elements of venous wall, being much thicker than the original vein wall.

a patent lumen in all grafts and it was not possible to identify a distinct vein segment between ureter and bowel. Several sections were cut from each specimen for microscopic study and after formalin fixation they were stained with hematoxylin and eosin and van Gieson-Weigert stains.

Microscopic examination of the sections revealed a narrowed lumen lined with transitional cell epithelium along the entire length of the original vein graft. The wall of the vein at four weeks had been invaded by proliferating fibroblasts and blood vessels growing from the ureter and sigmoid and surrounding tissues but the elastic fibers, as demonstrated by van Gieson-Weigert stain, were intact. Some valve leaflets were covered with transitional cell epithelium. The vein segment was considerably shortened and the wall thickened. At six weeks, fibroblastic activity was more pronounced and the vein wall was replaced by fibrous tissue with distortion and clumping of the elastic fibers. At eight weeks, vein wall could no longer be identified and the channel lined with transitional cell epithelium was surrounded by a thickened mass of fibrous tissue. Elastic fibers were present but they were clumped near the sigmoid end of the graft and were less numerous than those seen on earlier sections. Valve leaflets were still seen. Figure 5, *A* is a photomicrograph (H and E  $\times 100$ ) of the ureterovenous junction in an animal sacrificed 6 weeks after operation. There is transitional cell epithelium lining the narrow channel which funnels from the dilated ureteral lumen. Many fibroblasts invade the venous tunics but the epithelium is intact. Figure 5, *B* shows a vein graft (van Gieson-Weigert  $\times 50$ ) 8 weeks after operation. The channel is almost obliterated and there is contraction of the graft with clumping of the elastic fibers in the distal portion of the vein. The wall of the vein has been almost entirely replaced by fibrous tissue and is much thicker than the original vein wall.

*Ureteroveno-ureterostomy.*—Four dogs were studied in this portion of the experiment. A segment of the middle third of the left ureter was resected without clamps and replaced by an equivalent length of vein. Common femoral vein was utilized in two instances with two and four centimeter segments of vein being used. Twice external jugular vein was used with a length of six and ten centimeters respectively. A simple end-to-end anastomosis was performed using 4 sutures at each end. Arterial silk No. 000000 was used in 2 dogs, being careful to avoid the mucosa and atraumatic No. 0000 chromic gut sutures were used in the other 2 animals. The direction of the valves was such that urine would flow down the ureter but reflux from the bladder would be prevented. Urine flowed freely through the vein graft at the completion of the operation and there was no visible leakage.

All 4 animals remained clinically well until they were sacrificed three, 4, 6 and 8 weeks after operation. However, excretory urograms revealed beginning obstruction in 2 weeks which was complete after 4 weeks. Figure 6 is the pyelogram of a dog having a femoral vein graft 4 cm. long, 4 weeks after operation. Third degree hydronephrosis and hydro-ureter are present.

Autopsy of the animals revealed marked hydronephrosis and hydro-ureter in all specimens. The point of obstruction was the cephalad junction of ureter and

vein. The vein segment was contracted to less than five millimeters in each instance and the original length of vein did not influence the ultimate fate of the graft. The graft itself was a short, bony-hard cord with about twice the circumference of the original vein. Below the fibrous segment the distal ureter was normal. None of the grafts was patent.

Microscopic examination of the anastomotic site revealed bone formation and fibrosis with replacement of the vein in every instance regardless of whether or not absorbable suture material had been used. Figure 7, *A* shows a section through the cephalad ureterovenous junction four weeks after operation (van Gieson-Weigert  $\times 50$ ). There is marked hydro-ureter with a dilated lumen lined



FIG. 6. Left ureteroveno-ureterostomy 4 weeks after operation. Four centimeter segment of femoral vein used to repair a defect in middle third of ureter.

with transitional cell epithelium. A layer of bone lies between the ureter and vein. The wall of the vein shows marked fibroblastic proliferation with the strata of distorted elastic fibers also being invaded by fibroblasts. Figure 7, *B* (*H* and *E*,  $\times 100$ ) demonstrates the marked amount of fibroblastic proliferation present in the vein segment 6 weeks postoperatively. Ureteral epithelium is seen in the upper portion of the photomicrograph and there is a well outlined bone island. There is no longer any lumen in the graft. Figure 8 (van Gieson-Weigert  $\times 50$ ) points out the gnarled, contracted mass of elastic fibers in the lower portion of the photomicrograph. At this stage, 8 weeks after operation, there is dense fibrosis without discernible venous cellular tissue except for the distorted elastic fibers which are being invaded by fibrous tissue from the periphery.

*Ureterovenocystostomy.*—Only 2 dogs have thus far been studied for healing after this procedure. The technique used was similar to that in the ureterovenenterostomies. The left ureter was cut 2 cm. proximal to its bladder insertion, a



FIG. 7. *A*, photomicrograph (van Gieson-Weigert  $\times 50$ ) of cephalad ureterovenous junction 4 weeks after ureterovenoureterostomy. Marked hydro-ureter is present. Bone surrounds transitional cell epithelium. Fibroblastic proliferation and elastic tissue are present throughout the wall of vein. *B*, photomicrograph (H & E  $\times 100$ ) of venous autograft 6 weeks after ureterovenoureterostomy. Ureteral epithelium is seen in upper right corner of field. Marked fibroblastic activity surrounds well outlined bone island.

2 cm. segment of femoral vein was sutured to the proximal end of the ureter by No. 0000 atraumatic chromic gut sutures in a simple end-to-end anastomosis, the distal ureter ligated, the caudal end of the vein segment then anastomosed to the bladder through a small stab wound in the bladder and a mucosa-to-mucosa anastomosis performed with the full thickness of vein and bladder being included in each suture. Urine flowed through the vein into the bladder at the completion of the experiment and there was no visible leakage.

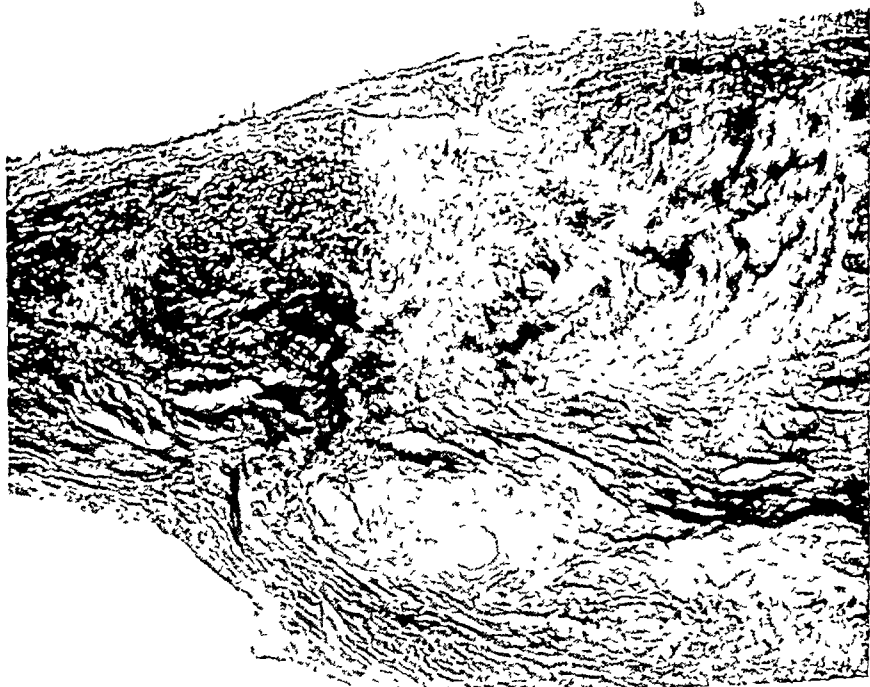


FIG. 8 Photomicrograph (van Gieson-Weigert  $\times 30$ ) of vein autograft 8 weeks after ureteroveno-ureterostomy. Dense fibrous tissue replaces cellular elements of vein. Lower portion of graft shows large gnarled mass of elastic tissue with fibroblastic invasion from periphery.

Both animals remained well clinically for approximately 48 hours when they began to refuse food and vomited frequently. Each died on the fourth postoperative day and autopsy revealed sloughing of the distal end of the vein graft with leakage into the peritoneal cavity from the bladder. No definite conclusions can be drawn from this portion of the experiment since the series was too small and the animals did not survive long enough to permit detailed observation of the fate of the venous autograft in the distal portion of the ureter. Perhaps the marked variation in bladder size with filling and emptying or lack of adequate blood supply to the vein from the canine bladder were among the factors predisposing to leakage and necrosis.

#### DISCUSSION

The fate of the venous autograft in ureteroveno-enterostomy is similar to that of the vein grafts used for the repair of common bile duct defects. When a 2

cm. length of vein is anastomosed between the distal ureter and sigmoid. blood supply to the graft is adequate to prevent necrosis so that sloughing does not occur. In every case the vein segment became lined with transitional cell epithelium. The marked contraction to less than 5 mm. with fibroblastic replacement of the vein wall may possibly be due to the response of adjacent ureteral and sigmoidal fibroblasts to the presence of a foreign tissue such as would be the fibroblastic response to a foreign body. In fact, Blakemore and Lord<sup>24</sup> reported a similar response when vein homografts were used in experimental arterial surgery. Since we were unable to cause reflux of urine in any instance and patency of the vein grafts was proven, the venous valvular system may remain partially competent. Hydro-ureter and hydronephrosis most likely occurred because of a strictured lumen in the vein segment with lack of peristalsis. The significance of urine in the production of fibrosis in the venous autograft is not yet known. Since the lumen of the graft remains surrounded by epithelium and fibrous tissue invades the graft from the periphery, urine itself is probably not an important factor. Studies are now in progress of venous grafts in uretero-enterostomy where the urine has been diverted at least until complete healing occurs.

Nutritive factors undoubtedly play a part in the fate of the vascular auto- or homograft. McCune and his co-workers<sup>25</sup> demonstrated by India ink injection that practically all of the circulation reaching the wall of the arterial graft is derived from surrounding tissues. Blood supply to the graft from the anastomosis at the graft ends occurs to a small extent only. When the grafts were wrapped in cellophane, the portion of the wall adjacent to the lumen remained more normal than that of the outer media and adventitia where necrosis occurred. This indicates that some nutrition passes through the endothelium from the lumen. In our experiments, no effort was made to surround the graft with vascular tissue and the lumen of the vascular graft in the ureter is bathed with urine rather than nutritive blood.

In ureteroveno-ureterostomy, complete obstruction with heterotopic bone formation occurred in every case. Bone formation was limited to the areas adjacent to the epithelium. Inadequate blood supply to the graft may be a factor contributing to osteogenesis and adequate blood supply may be the reason why no bone was formed in any of the ureterovenoenterostomies. The peculiar osteogenetic properties of upper urinary tract epithelium have been observed previously and Abeshouse<sup>26</sup> has summarized the work in this field. Strauss<sup>27</sup> demonstrated the osteogenetic properties of urothelium by transplanting flaps of transversalis muscle, fascia and peritoneum to the ureters of dogs. Bone formed in the portion of the flap bordering on the ureteral lumen. Neuho<sup>28</sup> and Phemister<sup>29</sup> transplanted fascia lata to dog bladders and also observed bone formation along the graft next to the bladder epithelium. Ossification did not occur in the same experiments in rabbits and sheep which have an alkaline urine.<sup>30</sup> Huggins<sup>31</sup>

<sup>25</sup> McCune, W. S., Tliglethwaite, J. R., Keshishian, J. M. and Blades, B.: *Surg. Gynec. & Obst.*, 84: 311-316, 1952.

<sup>26</sup> Abeshouse, B. S.: *J. Urol.*, 39: 50-63, 1945.

<sup>27</sup> Strauss, A. A.: *Surg. Gynec. & Obst.*, 15: 75-84, 1914.

<sup>28</sup> Neuho, H.: *ibid.*, 24: 383-427, 1917.

<sup>29</sup> Phemister, D. B.: *Ann. Surg.*, 78: 232-249, 1923.

<sup>30</sup> Huggins, C. B.: *Proc. Soc. Exper. Biol. & Med.*, 27: 342-351, 1930.



found that bone formed even though the urine had been diverted so that urine itself was eliminated as a factor. Transplants of bladder, ureteral or renal pelvic mucosa to parietal fasciae also produced bone. This type of heterotopic bone formation is presumably due to metaplasia of the proliferating epithelium and connective tissue. Abeshouse<sup>23</sup> maintains that the two main factors involved are epithelium with osteogenetic stimulating power and ossifying fibroblasts.

At the present time, the use of venous autografts in uretero-enterostomy or in other ureteral surgery is not practical. However, only by observation of the biological response of tissues to autologous or homologous grafts can an understanding develop of the specific processes involved in the production and prevention of fibrosis in grafts of this kind. Tissue culture methods and studies of acquired immunity factors may provide information about cell metabolism which will help overcome tissue incompatibilities.

#### SUMMARY

Fresh autogenous vein grafts have been studied experimentally in the repair of ureteral defects and the venous valvular system has been used for the prevention of the ureteral reflux of feces in ureterosigmoidostomy and of bladder urine in ureterocystoneostomy.

In the 6 cases with ureterovenosigmoidostomy, the vein lumen became narrowed and was lined with transitional cell epithelium. The vein graft in all instances was markedly shortened and the cellular elements of the autograft wall were replaced by a reactive ingrowth of fibroblasts from the tissues adjacent to the graft. The elastic fibers persisted but were distorted by fibroblastic invasion. There was partial obstruction to the flow of urine in every case although reflux of feces was prevented.

In all 4 dogs with ureteroveno-ureterostomy, heterotopic bone formed next to the ureteral epithelium. Complete occlusion of the graft occurred with fibroblastic replacement of the entire vein wall except for some of the elastic tissue.

The two experiments with ureterovenocystostomy could not be studied for the ultimate fate of the autograft. Leakage and sloughing of the distal end of the graft occurred after 48 hours.

## A STUDY OF HYDRODYNAMICS OF THE UPPER URINARY TRACT FOLLOWING URETEROSIGMOIDOSTOMY

CARL F. RUSCHE AND WELLS C. COOK

One of the most perplexing problems following uretero-intestinal anastomosis is the mechanism of electrolyte imbalance. The advent of chemotherapy, antibiotics and the replacement of blood has sharply reduced the immediate post-operative mortality. However, there has not been a corresponding decline in the incidence of postoperative morbidity. A considerable amount of investigation, particularly during the last decade, has demonstrated that the morbidity is associated with an electrolyte imbalance manifested by acidosis.

Children with exstrophy of the bladder upon whom a successful transplantation of the ureters to the rectosigmoid has been carried out, survive in good health from 10 to 25 years. Patients with only one kidney which drains through a nephrostomy, or those with ureterocutaneous transplantation, do not have electrolytic disturbances. Twenty per cent of adults are living in comparative comfort and maintaining satisfactory electrolyte balance regardless of clinical management or the type of ureteral anastomosis performed.

Several theories have been advanced as to the cause of electrolyte disturbance, the most popular being the theory of absorption of the urinary constituents from the intestine. However, Lapides' investigations have revealed that the chemical imbalance is caused by a dual mechanism. The renal tubular damage is the primary cause of electrolyte disturbance with intestinal absorption of urinary constituents playing a secondary role.

Several approaches for the correction of this problem have been carried out. Perhaps one of the most enlightening investigations was made by Ferris and Odel relative to absorption of the urinary constituents from the intestine, who postulated the occurrence of a selective rectal absorption of chlorides, producing a relative sodium deficiency and acidosis. However, they failed to explain the elevated levels of blood urea. Sauer found a rise in the blood urea nitrogen when patients were on constant rectal tube drainage, and a fall when the rectal tube was removed. Boyce and Vest demonstrated that any decrease in tubular function, resulting from either back pressure or pyelonephritis, will accentuate the electrolyte imbalance. The bacterial content of the colon, which is always markedly increased in the presence of urine, has a tendency to increase acidosis. Hinman has beautifully demonstrated the renal changes associated with the mechanism of pyelorenal backflow and he found that the pressure required to produce backflow in normal kidneys varied considerably, from 20 to 120 mm mercury (260 to 1820 cm. of water.) He also demonstrated that a much lower pressure was required to produce the same result in the hydronephrotic kidney, 9 to 16 mm. mercury (120 to 200 cm. of water.) Boyce and Vest found that the average resting intrarectal pressure was 27 cm. of water, and during defecation the pressure may rise to 270 cm. of water. They showed that the urge to defecate

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 21, 1952.

does not occur until the pressure in the bowel has arisen from 50 to 70 cm. of water.

Whisenand and Moore suggested that the obstruction to urine outflow as the result of intrarectal pressure may finally produce an impairment of renal function with retention of nitrogen. Their report of a case relative to hydrodynamics of the upper urinary tract following mucosal ureterosigmoidostomy, prompted us to be on the alert for a patient upon whom further investigations could be made to determine whether the intrapelvic pressures transmitted from the colon play a role in the production of renal infection, which apparently precedes acidosis and hyperchloremia in cases with diversion of the urinary stream to the colon. The following report is relevant to a patient with an acquired absence of a kidney, with a nephrostomy in the remaining kidney, upon whom a ureterosigmoidostomy was performed.

#### CASE REPORT

A. H. (C30493) a white male, aged 67, was admitted to the hospital October 12, 1949, complaining of pain in the left kidney region, referred to the corresponding groin and testicle, of 3 weeks' duration. There was an accompanying anorexia and a 12 pound weight loss. The family and past history were noncontributory.

The physical examination was essentially normal except for moderate tenderness in the left costovertebral angle and along the course of the left ureter. The prostate was enlarged to grade 2 with some induration noted in the region of the left seminal vesicle. The blood pressure was 168 systolic and 96 diastolic. The temperature and pulse were normal. Blood studies revealed hemoglobin 14.4 gm.; red blood cells 4.5 millions; white blood cells 9,450; nonprotein nitrogen 28 mg. per 100 cc of blood. The blood serological test was negative. The urine was negative. Roentgenograms of the chest were normal. A cystoscopic examination disclosed intravesical prostatic hyperplasia, grade 2, and a flat sessile vesical neoplasm, 2 by 2 cm., near the left ureteral orifice. A biopsy of the lesion revealed epidermoid carcinoma, grade 4.

Differential function studies revealed marked reduction in function of the left kidney with good function of the right. Both the excretory and retrograde pyelograms showed a constant filling defect in the right kidney consistent with neoplasm. The left kidney disclosed a duplication with bifurcation of the ureter. There was present a large left hydronephrosis and hydro-ureter. A filling defect of the bladder was consistent with intravesical enlargement of the prostate and questionable new growth.

Surgical exploration of the left kidney was carried out September 16, 1949. It was found to be markedly dilated and a nephrostomy was performed. Nephrostomy pyelograms on the 11th postoperative day revealed improved function.

On November 3, 1949, the right kidney was surgically explored and removed because of a questionable malignancy. However, gross section of the specimen revealed a solitary cyst. On January 18, 1950 an open resection of the vesical tumor with implantation of radon seeds was carried out.

During the next 8 months the patient made satisfactory progress. At this time

repeated pyelographic studies through the nephrostomy demonstrated complete obstruction of the pelvic ureter. A left ureterosigmoidostomy was advised and accepted by the patient. Physically the patient was in good health. The temperature was 98.6; blood pressure 149 systolic, 70 diastolic. The hemoglobin was 13.5 gm.; erythrocytes 4.5 million; leukocytes 8,950, total proteins 6.5 with a normal albumin globulin ratio. The nonprotein nitrogen was 44 mg. per 100 cc of blood. The electrocardiographic findings were normal. Cystoscopy revealed a normal bladder, with no evidence of the tumor which had been previously resected.

On October 14, 1950, a left ureterosigmoidostomy was carried out using the mucosa-to-mucosa technique. The postoperative course was uneventful with the highest recorded temperature, 99.6 F. Following the anastomosis, flatus and fecal material escaped from the nephrostomy.

Subsequent pyelograms through nephrostomy demonstrated free communication between ureter and bowel (fig. 1).

Ten days preceding death, and 14 months after the ureterosigmoidostomy, the patient complained of marked obstipation with an increased amount of fecal drainage through the nephrostomy. Enemas were ineffectual; therefore, 4 ounces of citrate of magnesia were given orally and within 2 hours the patient complained of severe epigastric pain accompanied by profound shock, and died 13 hours later.

The autopsy revealed a rupture of the duodenum with generalized peritonitis. The bowel obstruction was produced by extensive retroperitoneal metastases, which involved the rectum and the sigmoid producing a complete obstruction. The metastases extended along the ureter up to and including the hilus of the kidney. There was no dilatation of the kidney or ureter. Microscopic sections from the kidney showed diffuse pyelonephritis with marked changes in the renal tubules. The bladder showed no gross evidence of tumor and the mucosa was intact.

Microscopic sections taken from the perivesical tissues and mass surrounding the sigmoid, rectum, and ureter, revealed the same tumor which had been noted previously in the bladder biopsy (epidermoid carcinoma grade 4). Metastases were not demonstrated in any of the other organs in the body.

Manometric determinations of the colon and intrarenal pressures were started 5 weeks following the uretero-intestinal anastomosis and continued until death. An attempt was made to correlate the blood findings with pressure changes during the same interval.

The manometric studies showed simultaneous renal and bowel pressures. When the nephrostomy was closed for 96 hours and the bowel not emptied for 3 hours prior to study, the bowel pressure was found to be equal or greater in most instances. Both the bowel and renal pressures returned immediately to the initial levels when the bowel and kidney were emptied; however, on over-distention of either the renal pelvis or rectosigmoid, the initial pressure was not achieved for 10 minutes. Overdistention of the bowel produced cramping, resulting in peristaltic rushes; nevertheless, these pressures were not transmitted to the kidney.

A study was made after the patient had been on nephrostomy drainage for 48 hours and there was an urge to defecate. The pressure in the colon was 23 cm. of water, and intrarenal pressure was 31 cm. of water. When the patient was completely relaxed or in a 25 per cent Fowler's position, there was lowering of both



10-25-50

FIG. 1. Radiogram 12 days following ureterosigmoidostomy demonstrating free communication between ureter and colon.

pressures; when the patient strained or was placed in a 50 per cent Fowler's position or more, there was an associated rise in both pressures to 35 cm. (fig. 2).

When the nephrostomy was closed for 48 hours and the bowel emptied before the pressure determinations, the same pressure relation existed between the bowel and kidney except at a slightly lower level (fig. 3). Blood chemistry determinations were made concurrently with the manometric studies. These include daily



nonprotein nitrogen and  $\text{CO}_2$  combining power, with interval determinations of blood chlorides, creatinine and potassium.

The first study carried out after the nephrosotomy was clamped for 96 hours revealed an initial nonprotein nitrogen of 58 mg. per 100 cc of blood; the  $\text{CO}_2$  combining power was 25. After nephrostomy drainage for 10 days the nonprotein nitrogen returned to 30 mg. per cent, and the  $\text{CO}_2$  combining power to 50 volumes per cent. During the same interval the blood chlorides remained elevated to 635. In the last 3 days of the study, all of the urine collected from the nephrostomy was replaced into the rectum and the patient instructed to retain the urine as long as possible. During this period there was a fall in the nonprotein nitrogen, and a rise in the  $\text{CO}_2$ .

After closing the nephrostomy for 4 days the nonprotein nitrogen rose from 50 mg. to 94 mg. and the  $\text{CO}_2$  dropped from 47 volumes per cent to 20 volumes per cent. When the nephrostomy was opened daily for 2 hours, there was a prompt elevation of the  $\text{CO}_2$ ; however, the nonprotein nitrogen levels remained consistently above normal. When the nephrostomy was opened from 10 to 12 hours daily, the nonprotein nitrogen and  $\text{CO}_2$  returned and remained within normal limits.

The patient enjoyed good general health but the study was terminated December 20, 1951, nine days before the patient's death, because of marked obstipation, abdominal distension, and increased fecal drainage through the nephrostomy.

#### DISCUSSION

The renal pressure was 3 to 5 cm. higher than the bowel pressure, except during straining or when the position varied from 60 per cent Fowler's to horizontal. When the nephrostomy tube was opened and the renal pelvis emptied, 3 to 4 minutes were required for the renal pressure to return to the former level.

The intrarenal pressure was not dependent on the length of time the nephrostomy was closed. Cramping associated with a desire to evacuate produced an elevation of colonic pressure, and in most instances, it was higher than the intrarenal pressure. The reverse was true shortly following the evacuation of the bowel. From this study one could hardly conclude that the colonic pressure is sufficiently high to produce either the mechanism of pyelorenal backflow or a retention of urea. However, it is possible to conclude that without an adequate mechanism between the colon and ureter the occasional elevation of pressure in the bowel may definitely increase the danger of renal infection resulting in impaired renal function.

The changes in the blood urea and  $\text{CO}_2$  combining power in this patient followed closely the pattern so frequently observed clinically after diversion of the urinary stream to the colon. Whenever the nephrostomy was closed for 24 hours or longer there was laboratory evidence of acidosis. However, when the nephrostomy was open 8 to 10 hours daily acidosis did not occur. The passage of gas and often times fecal material through the nephrostomy produced no changes in the patient's clinical course or blood findings. The patient's course was unusual; he was entirely free from fever, maintained a good appetite and gained weight while under observation.

## SUMMARY

A case of a patient with carcinoma of the urinary bladder, with an acquired ab-sence of one kidney, and a nephro-tomy in the remaining kidney, upon whom a uretero-igmoidostomy was performed, is pre-sented. Further evidence that ureterorenal reflux occurs in patients following uretero-igmoidostomy is supplied, together with the results of the reflux in 1 case. Simultaneous water manometric determinations of colon and renal pressures were made, and pressures found which were lower than those previously reported.

The findings would tend to disprove the impression that colonic pressures are sufficiently high to produce the mechanism of pyelorenal backflow or that this is the direct cause of retention of urea, but they may play a role in the production of renal infection.

The electrolyte changes in the blood were recorded at weekly intervals from the time of the uretero-igmoidostomy until a short time before the death of the patient.

It is concluded, in view of all the experimental work reviewed and the additional observations on the effect of pressure changes in the colon or renal pelvis, that there is a combination of factors operating in the production of the acidotic state.

*Taft Bldg., Los Angeles, Calif.*

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nonprotein nitrogen and  $\text{CO}_2$  combining power, with interval determinations of blood chlorides, creatinine and potassium.

The first study carried out after the nephrosotomy was clamped for 96 hours revealed an initial nonprotein nitrogen of 58 mg. per 100 cc of blood; the  $\text{CO}_2$  combining power was 25. After nephrostomy drainage for 10 days the nonprotein nitrogen returned to 30 mg. per cent, and the  $\text{CO}_2$  combining power to 50 volumes per cent. During the same interval the blood chlorides remained elevated to 635. In the last 3 days of the study, all of the urine collected from the nephrostomy was replaced into the rectum and the patient instructed to retain the urine as long as possible. During this period there was a fall in the nonprotein nitrogen, and a rise in the  $\text{CO}_2$ .

After closing the nephrostomy for 4 days the nonprotein nitrogen rose from 50 mg. to 94 mg. and the  $\text{CO}_2$  dropped from 47 volumes per cent to 20 volumes per cent. When the nephrostomy was opened daily for 2 hours, there was a prompt elevation of the  $\text{CO}_2$ ; however, the nonprotein nitrogen levels remained consistently above normal. When the nephrostomy was opened from 10 to 12 hours daily, the nonprotein nitrogen and  $\text{CO}_2$  returned and remained within normal limits.

The patient enjoyed good general health but the study was terminated December 20, 1951, nine days before the patient's death, because of marked obstipation, abdominal distension, and increased fecal drainage through the nephrostomy.

#### DISCUSSION

The renal pressure was 3 to 5 cm. higher than the bowel pressure, except during straining or when the position varied from 60 per cent Fowler's to horizontal. When the nephrostomy tube was opened and the renal pelvis emptied, 3 to 4 minutes were required for the renal pressure to return to the former level.

The intrarenal pressure was not dependent on the length of time the nephrostomy was closed. Cramping associated with a desire to evacuate produced an elevation of colonic pressure, and in most instances, it was higher than the intrarenal pressure. The reverse was true shortly following the evacuation of the bowel. From this study one could hardly conclude that the colonic pressure is sufficiently high to produce either the mechanism of pyelorenal backflow or a retention of urea. However, it is possible to conclude that without an adequate mechanism between the colon and ureter the occasional elevation of pressure in the bowel may definitely increase the danger of renal infection resulting in impaired renal function.

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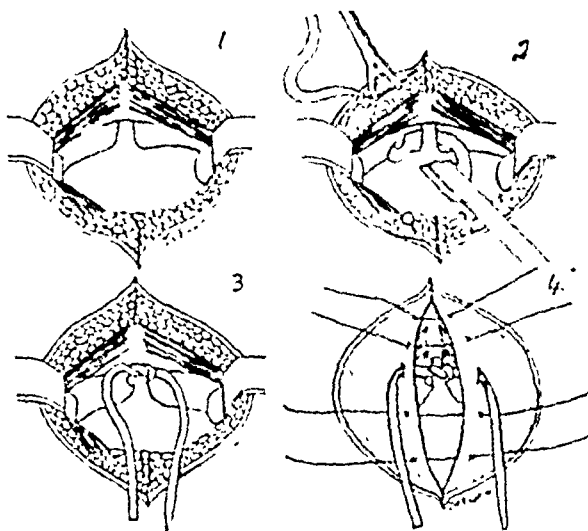


FIG. 1

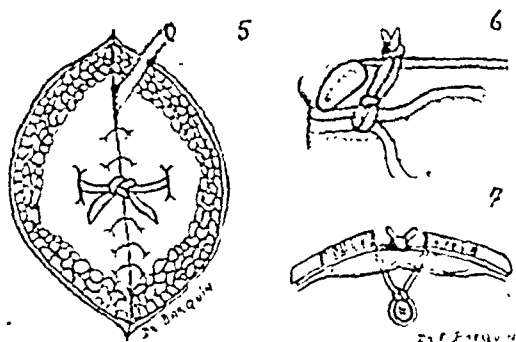


FIG. 2

urethra and anterior vaginal wall by means of a blunt boomerang needle (fig. 1, 2). The ribbon gut is knotted with double knots securing the first with a needle holder until the second can be tied; the knots are tied snugly so as not to strangle the urethra over the catheter (fig. 1, 3). The free ends of the ribbon gut are drawn through two button holes in middle of the recti muscles and fascia (fig. 1, 4). A Penrose drain is inserted in the space of Retzius and fascia closed with No. 2 chromic interrupted sutures, and the loose ends of the ribbon gut tied over the fascia (fig. 2, 5), and the rest of the wound is closed as usual. The vaginal pack is removed and the Foley catheter is left in place for 10 days.

We have followed this technique in 15 (and one man in the 14) cases of stress incontinence with excellent results.

Figure 2, 6 shows how the vesical neck is elevated by the ribbon gut. Figure 2, 7 shows how the urethral sling is fixed in the anterior abdominal wall.

## A SURGICAL TECHNIQUE FOR STRESS INCONTINENCE IN WOMEN: MODIFICATION OF MILLIN'S TECHNIQUE

F. BARQUÍN, A. PEREIRA AND L. BAY

Stress incontinence in women is a notoriously common condition which greatly incapacitates them, particularly in their marital life, and often leads to a neurosis.

The condition is found mostly in women who are in or have passed the fourth decade of life. It is most commonly due to postpartum injuries which are not revealed until later in life when supporting tissues begin to lose their elasticity; also to excessive loss of weight, avitaminosis, endocrine and neurological changes of menopause.

In reviewing the procedures for correction of incontinence in the female, we find that the first surgical technique was presented by Goebell<sup>1</sup> in 1910, which was later modified by Frangenheim<sup>2</sup> in 1914, and again by Stoeckel<sup>3</sup> in 1917. Today it is known in gynecology and urology by Goebell-Frangenheim-Stoeckel technique. This was modified by Miller in 1932 and again by Aldridge<sup>4</sup> in 1942. Kelly's<sup>5</sup> operation, mattress suturing of the vesical neck and sphincter, of 1914, was modified by Kennedy in 1937.

Mr. Terence Millin, in his book, *Retropubic Urinary Surgery*, published in 1947, presents his technique supra- or retropubic approach for the correction of stress incontinence in women.<sup>6</sup>

We have utilized Millin's procedure in 4 cases, and have modified the technique due to the fact that in 2 cases we found the aponeurosis too friable to use to elevate the vesical neck, and in our technique we have substituted ribbon gut for aponeurosis.

A 5 cc No. 16 Foley catheter is introduced along the urethra into the bladder, and the vagina is packed with sterile gauze.

This facilitates the separation at the line of cleavage between the posterior aspect of the urethra and anterior vaginal wall. A low midline incision is made from just below the umbilicus to two centimeters above the superior border of the symphysis pubis to the aponeurosis of recti (fig. 1, 1). The aponeurosis is opened in midline, the recti muscles separated and are held separated by a self-retaining retractor. The fatty tissue and peritoneal fold are drawn upwards by blunt dissection, utilizing the index finger of right hand. Using small swabs on a Kocher forceps, the anterior vesical wall and bladder neck are cleansed of perivesical fat. With the index finger of the right hand, blunt dissection is started along the right side of bladder neck and between urethra and anterior vaginal wall. When dissection has been completed, ribbon gut is passed between the

<sup>1</sup> TeLinde, R. W.: *Operative Gynecology*. Philadelphia: J. B. Lippincott Co., 1946, p. 174.

<sup>2</sup> J. A. M. A., 98: 528, 1932.

<sup>3</sup> Am. J. Obst. & Gynec., 44: 398-411, 1942.

<sup>4</sup> Urol. & Cutan. Rev., 17: 291, 1944.

<sup>5</sup> Am. J. Obst. & Gynec., 33: 19, 1937.

<sup>6</sup> Millin, T.: *Retropubic Urinary Surgery*. Baltimore: Williams and Wilkins, 1947, pp. 184-193.

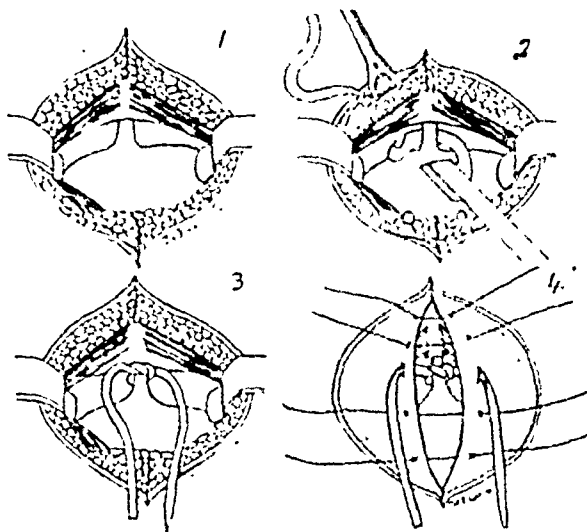


FIG. 1

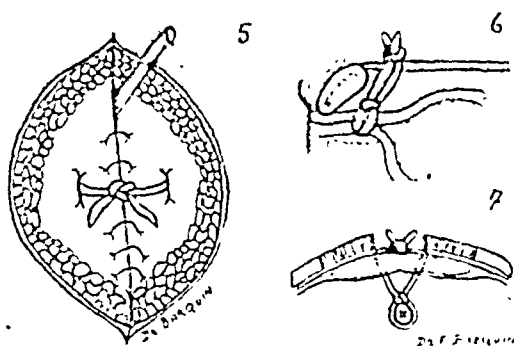


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17 St., No. 608, Vedado, Havana, Cuba

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<sup>3</sup> Am. J. Obst. & Gynec., 44: 398-411, 1942.

<sup>4</sup> Urol. & Cutan. Rev., 17: 291, 1914.

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will not completely eradicate such a neoplasm. Total cystectomy by sharp dissection through pelvic structures peripheral to the bladder has not been practiced and would be beset by grave technical difficulties. There is no analogy between total cystectomy, as now practiced, and Halsted's eminently successful total mastectomy. The latter gives the neoplasm a wide berth. The present form of total cystectomy gives the bladder tumor which has extended beyond the bladder wall less than no berth at all. The plane of dissection is directly across the avenue of invasion. Oversight of this difference between the radical operation for breast cancer and total cystectomy for bladder cancer probably accounts for misplacing hope in cystectomy.

Usually the avenue of invasion of a bladder tumor is relatively narrow, but often it extends far out into the pelvis from its comparatively limited area of origin in the bladder. Destruction of the neoplasm to the far end of its avenue of invasion is necessary for cure. If there is extension beyond the bladder wall this will not be accomplished by cystectomy. Moreover, there is no need for removal of bladder wall far peripheral to the tumor bearing surface area in the bladder from the center of which the outward invasion extends.

Electrocoagulation is capable of destructive heat penetration outward into surrounding structures from the surface area of bladder involvement to almost any desired extent—far beyond any sharp dissection which may be made.

In the long experience of one of us (FEBF), cutting current excision followed by deep electrocoagulation of the area of deepest invasion has given by far the best results of any method employed against deeply infiltrating bladder tumors. Former use of the method was conditioned by fear of postoperative pulmonary embolism due to heat coagulation of blood in the comparatively large adjacent and neighboring veins. The extent of heat penetration was deliberately limited to avoid this effect. In spite of that precaution fatal pulmonary embolism occurred in 3 cases and dictated still more cautious use of the agent.

It has been long known that the vena cava may be ligated anywhere between the iliac bifurcation and the renal veins with only temporary ill effects in the form of lower extremity edema. In recent years, deliberate and purposeful cava ligation has been employed in the treatment of thrombophlebitis of the lower extremities and by gynecologists in connection with extensive pelvic operations. These deliberate uses of cava ligation suggested its employment as a prophylactic measure against pulmonary embolism in connection with massive electrocoagulation of deeply infiltrating bladder tumors. It appeared that prevention of embolism in this way would safely permit much more extensive heat destruction of bladder tumors than had been previously permissible and would make feasible eradication of neoplastic invasions of surrounding structures not removable by dissection and not destroyed by the limited application of electrocoagulation formerly employed.

#### METHOD

*Electrocoagulation* should be sharply distinguished from *fulguration* (fig. 1). Both of them are effected by high frequency current. In the case of fulguration

## MASSIVE ELECTROCOAGULATION OF DEEPLY INFILTRATING BLADDER TUMORS COMBINED WITH LIGATION OF THE VENA CAVA FOR PREVENTION OF PULMONARY EMBOLISM

FREDERIC E. B. FOLEY, EDWARD J. RICHARDSON, WILLIAM P. MULVANEY  
AND IRVING VICTOR

Bladder tumors have wide ranges of character in respect of different features. The surgical problem posed by bladder tumors is defined by the character of the neoplasm with respect to: 1) cytologic type, 2) extent of surface area involvement, 3) depth of invasion and 4) metastatic involvement.

A very simple surgical problem is posed by the benign bladder tumor with small surface area of involvement, without invasion beyond the mucosa and without metastasis. There is general agreement among urologic surgeons concerning management of such tumors. The surgical principles of general agreement encompass a variety of methods giving excellent results with tumors of this character and others substantially less innocent.

The surgical problem becomes more formidable and difficult in proportion to lack of cell differentiation, the extent of surface area involvement, depth of invasion and metastatic extension. Decrease in the percentage of surgical cures parallels the character of the tumor as indicated by the grades of these features.

There is general disagreement concerning the surgical management of highly malignant, extensive and deeply invading bladder tumors. During the past 10 years improvement of the surgical treatment of tumors of this character has been a chief concern of clinical research in urology. The new conceptions, tireless effort and devotion of many workers during this period have not only failed to compose the divergence of opinion but actually have increased it. Moreover, the results currently obtained are not substantially better than former results.

The considerations here presented are strictly limited to very bad bladder tumors: malignant, extensive and deeply infiltrating. It is believed that among the cases of bladder tumor here reported there would be no two year survivors by any former method of surgical treatment.

The safeguards of modern surgery: multiple transfusions, improved anesthesia, sulfonamides, antibiotics, improved techniques and other advances have permitted total cystectomy with bilateral ureterosigmoidostomy to become a routine procedure.

When total cystectomy came into vogue it was widely regarded as promise of a new era in the surgical treatment of vicious bladder tumors. There was reason to believe this was an ill-founded hope. A deeply invading growth which has gone beyond the bladder wall will not be completely eradicated by total cystectomy. Yet this is the type of growth for which cystectomy has been most enthusiastically urged and most widely employed. A tumor of such character has extended across the cleavage plane in which the bladder would be enucleated by total cystectomy. It is inevitable that total cystectomy, as now practiced,

Read before the Section on Urology, American Medical Association meeting, Chicago, June 1952.

The peritoneal cavity is opened by median incision from the pubic arch upward beyond the umbilicus. The peritonealized surface of the bladder is palpated to determine the extent and direction of neoplastic invasion. Palpation is made along the iliac vessels and cava to determine if metastatic lymph nodes are present and the liver is palpated. If there is no evidence of metastasis the contemplated procedure is carried out.

The posterior parietal peritoneum over the vena cava is incised. The cava immediately above its iliac bifurcation is bluntly separated from surrounding structures around its whole circumference and is ligated with umbilical tape.

The inspection and palpation have determined if there is invasion extending to the peritonealized surface of bladder wall. If such extension of the neoplasm

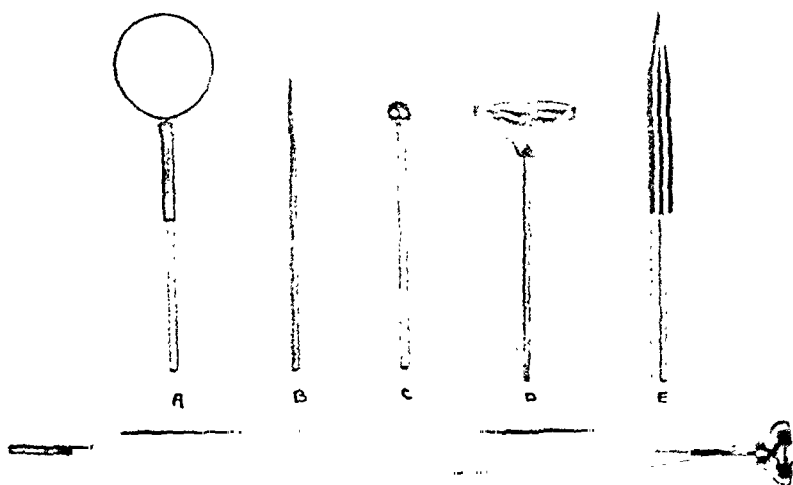


FIG. 2. Electrodes: A, cutting current loop. B, fulgurating point. C, fulgurating ball. D, coagulating stamp. E, coagulating spike.

is present the area of involvement is extraperitonealized by circular incision of the peritoneum peripheral to the area of involvement, dissecting up a peripheral flap of peritoneum and bringing its edges together by suture, thus extraperitonealizing the surface of involvement. If the tumor involves peritonealized portions of bladder without extension through the bladder wall, the peritoneum is only stripped away from the bladder without extraperitonealizing any part of its serosal surface.

The peritoneal cavity is closed and the bladder is opened. The presenting tumor is excised with the cutting current loop (fig. 2, A) carrying the excision deeply into the bladder wall. Around the periphery of the denuded area the excision will expose normal appearing muscle bundles. At the center of the denuded area the excision will not have reached through the central part of the invading growth. It is not important that the core of invading growth be excised. After control of bleeding by fulguration, the whole denuded area is subjected



the active electrode is held a short distance from the tissue. The current is made to arc from the active electrode to the tissue. The effect is superficial burning with carbonization. Nearly all of the energy is spent on the surface area struck by the arc and there is no significant heat penetration. In the case of electrocoagulation (diathermy, dielectric heating), the energy is applied in a different way. The active electrode is held in contact with the tissue. The tissue (dielectric) between the active and inactive electrodes is heated. The area of heat is in the form of a cone with the apex at the active electrode within the bladder and base at the inactive electrode over the patient's buttocks. Temperature elevation over any cross section area of the cone will be approximately in inverse proportion to the area of the conical section. What may be the temperature elevation of

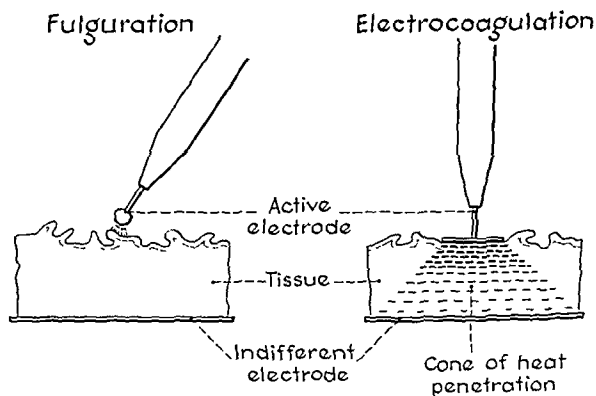


FIG. 1. Fulguration. Small, active electrode is held close to, but not in contact with, tissue. Current arcs from electrode to tissue. Nearly all of energy is spent on surface area struck by the arc. There is intense surface heat with carbonization, but no significant heat penetration.

Electrocoagulation. Comparatively large active electrode is held in contact with tissue. Energy is spent in gradual heating of the tissue (dielectric) between active and inactive electrodes.

Area of dielectric heating is in the form of a cone, with apex at the active electrode and base at the inactive electrode. Temperature elevation over any cross section of cone will be approximately in inverse proportion to area of section.

the tissue is evident from the fact that dielectric heaters or stoves with large electrodes of equal size will heat a large roast of meat to comparatively even coagulating temperature from surface to surface. Such temperature is lethal for the cells of both normal and neoplastic tissue.

Histologic examination shows that the thermal trauma of electrocoagulation extends beyond the area of local tissue coagulation. It extends through the venous, arterial and lymphatic channels. These are the avenues of extension of neoplasm. The fact that dielectric heating follows the same avenues may be significant.

#### CLINICAL APPLICATION OF METHOD

It has been determined from the cystoscopy, biopsy and rectal examination, with finding of a palpable mass, that the bladder tumor is 1) malignant, 2) extensive and 3) deeply infiltrating.

to 72 years. All of the tumors covered comparatively large surface areas. Eight of the tumors had extended through and beyond the bladder wall and belonged to Group C of the Jewett classification.<sup>1</sup> Two of the growths extended deeply into

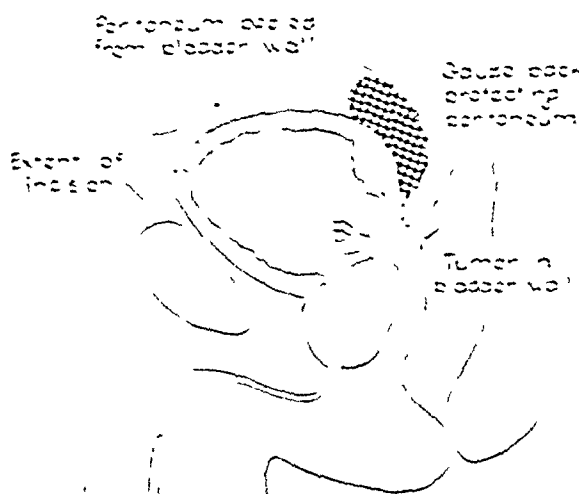


FIG. 4. Peritonium is stripped away from the underlying area of bladder wall. Gauze pack interposed between bladder and peritonium protects latter from destructive heat.

TABLE 1. *The effect of attempting to extirpate most of bladder, extent of excising, reflecting external bladder, and death or survival and interval between operation and finality of treatment.*

| CASE NUMBER | AGE | SIZE OF TUMOR         | EXTENT OF INCISION |                | TUMOR    | TIME INTERVAL BETWEEN OPERATION AND DEATH OR SURVIVAL |           | FINALITY OF TREATMENT |
|-------------|-----|-----------------------|--------------------|----------------|----------|-------------------------------------------------------|-----------|-----------------------|
|             |     |                       | Through wall       | Jewett class.  |          | Alive                                                 | Dead      |                       |
| 1           | 72  | 6 x 8                 | Yes                | C              | 16 Seeds |                                                       | 5 Months  | —                     |
| 2           | 67  | 4 x 5                 | Yes                | C              | No       |                                                       | 7 Months  | —                     |
| 3           | 59  | 4 x 4                 | Yes                | C              | 10 Seeds | 5 Years                                               |           | 0                     |
| 4           | 72  | 4 x 4                 | No                 | B <sub>2</sub> | 10 Seeds |                                                       | 8 Months  | 0                     |
| 5           | 61  | Right half of bladder | Yes                | C              | 8 Seeds  | 1 Year 7 Months                                       |           | 0                     |
| Female—6    | 69  | 4 x 6                 | Yes                | C              | 15 Seeds |                                                       | 11 Months | —                     |
| 7           | 67  | 5 x 5                 | No                 | B <sub>2</sub> | No       | 1 Year 4 Months                                       |           | 0                     |
| 8           | 61  | 3 x 5                 | Yes                | C              | No       | 1 Year                                                |           | 0 <sup>12</sup>       |
| 9           | 68  | 4 x 6                 | Yes                | C              | No       | 5½ Months                                             |           | 0                     |
| 10          | 69  | 7 x 7                 | Yes                | C              | No       |                                                       | 3 Months  | 0                     |

the bladder wall, but without gross evidence of perivesical involvement and belonged to Group B<sub>2</sub> of the Jewett classification. Of the 10 patients, six survive and four have died. The time interval between operation and the most recent cystoscopy or death were: 4 patients dead 5 months, 7 months, 8 months and 11 months after operation; 6 patients alive 3 years, 19 months, 16 months, 12

<sup>1</sup> Jewett, H. J. Carcinoma of the bladder. Influence of depth of infiltration on the 5 year results following complete extirpation of the primary growth. *J. Urol.*, 67: 672-676, 1952.

to massive electrocoagulation with a stamp electrode (fig. 3, *a*). Following that a spike electrode is plunged deeply into the core of the invading growth for a distance of two to three centimeters and is held in place while the coagulating current is supplied to the electrode (fig. 3, *b*). Arcing indicates that tissue in contact with the electrode has been carbonized and that maximal electrocoagulation of tissue peripheral to the electrode has been obtained. Closely spaced applications of this sort completely coagulate tissue far beyond the bladder wall over the whole area of involvement. During electrocoagulation of posterior wall tumors a gauze pack is placed between the bladder wall and the peritoneum which has been separated from it (fig. 4).

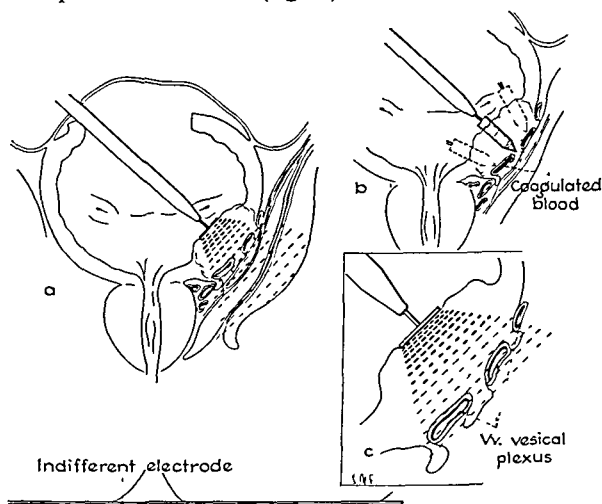


FIG. 3. Massive electrocoagulation of deeply infiltrating bladder tumor. *a*, Comparatively superficial electrocoagulation is effected by application of current with large surface area stamp electrode. Well below surface there is only dielectric heating without coagulation. *b*, Deep electrocoagulation is effected by application of current with a spike electrode inserted deeply into tissue. Well below surface there is complete coagulation including coagulation of blood in adjacent vessels whereas with more superficial coagulation effected by stamp electrode, *c*, "coagulation thrombi" are not formed in these vessels.

The coagulation of tissue and blood vessels far beyond the bladder wall, as described, would almost inevitably cause pulmonary embolism were it not for the cava ligation. The destruction of tissue thus accomplished extends far beyond the tissue removal which may be accomplished by cystectomy or any presently practiced sharp dissection. If the ureteral orifices and terminal portions of the ureters are in or close to the area of involvement they are included in the cutting current excision and electrocoagulation.

Ten bladder tumors without demonstrable evidence of metastasis have been subjected to the above described method of surgical treatment (table 1). All of these growths were regarded as inoperable by previous methods and beyond hope of complete eradication by cystectomy. All of the tumors were deeply infiltrating, undifferentiated squamous cell carcinomas of the bladder of large area. All of them belong to the class of bladder tumors, which according to the consensus of opinion are the most malignant and most nearly hopeless.

Among the 10 cases there were 9 males and 1 female. The ages were 60 years

to 72 years. All of the tumors covered comparatively large surface areas. Eight of the tumors had extended through and beyond the bladder wall and belonged to Group C of the Jewett classification.<sup>1</sup> Two of the growths extended deeply into

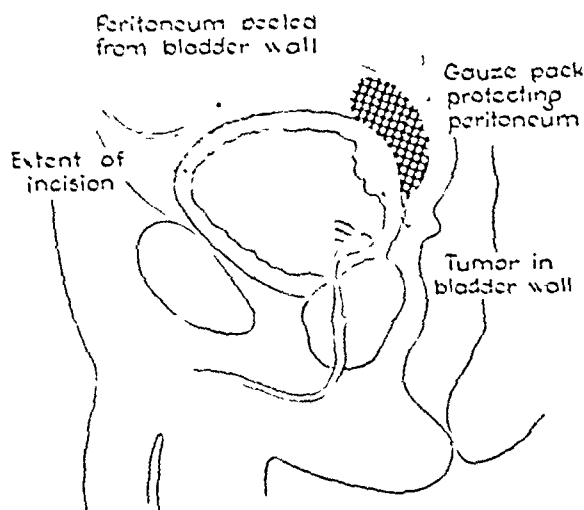


Fig. 4. Peritoneum is stripped away from tumor-bearing areas of bladder wall. Gauze pack interposed between bladder and peritoneum protects latter from destructive heat.

TABLE 1. Ten cases of malignant squamous cell carcinomas of bladder, extensive and deeply infiltrating treated by massive electrocoagulation and canal ligation for prevention of fatal pulmonary embolism

| CASE NUMBER | AGE | APPEARANCE            | INFILTRATION |                | FADON    | TIME SINCE OPERATION |           | TUMOR PRESENT |
|-------------|-----|-----------------------|--------------|----------------|----------|----------------------|-----------|---------------|
|             |     |                       | Thru wall    | Jewett class   |          | Alive                | Dead      |               |
| 1           | 74  | 6 x 8                 | Yes          | C              | 16 Seeds |                      | 5 Months  | —             |
| 2           | 67  | 1 x 5                 | Yes          | C              | No       |                      | 7 Months  | —             |
| 3           | 50  | 4 x 4                 | Yes          | C              | 10 Seeds | 3 Years              |           | 0             |
| 4           | 72  | 4 x 1                 | No           | B <sub>2</sub> | 10 Seeds |                      | 8 Months  | 0             |
| 5           | 61  | Right half of bladder | Yes          | C              | 8 Seeds  | 1 Year               |           | 0             |
| Female      |     |                       |              |                |          | 7 Months             |           |               |
| 6           | 69  |                       | Yes          | C              | 15 Seeds |                      | 11 Months | —             |
| 7           | 67  | 5 x 5                 | No           | B <sub>2</sub> | No       | 1 Year               |           | 0             |
|             |     |                       |              |                |          | 1 Months             |           |               |
| 8           | 61  | 3 x 5                 | Yes          | C              | No       | 1 Year               |           | 0 (?)         |
| 9           | 68  | 4 x 6                 | Yes          | C              | No       | 5½ Months            |           | 0             |
| 10          | 69  | 7 x 7                 | Yes          | C              | No       |                      | 3 Months  | 0             |

the bladder wall, but without gross evidence of perivesical involvement and belonged to Group B<sub>2</sub> of the Jewett classification. Of the 10 patients, six survive and four have died. The time interval between operation and the most recent cystoscopy or death were: 4 patients dead 5 months, 7 months, 8 months and 11 months after operation; 6 patients alive 3 years, 19 months, 16 months, 12

<sup>1</sup> Jewett, H. J.: Carcinoma of the bladder: Influence of depth of infiltration on the 5 year results following complete extirpation of the primary growth. *J. Urol.*, 67: 672-676, 1952.

months, 5½ months and 3 months after operation. In three of the fatal cases there was recurrent or persisting neoplasm. In 1 case, No. 4, death due to sepsis occurred 8 months following operation and the autopsy found no evidence of persisting or recurrent neoplasm.

The six surviving patients are well without evidence of neoplasm as determined by cystoscopy. However, one of these patients, case 8, now has unilateral exophthalmus which eventually may prove to be due to metastasis to the orbit.

In 5 cases radon seeds were implanted over the area of excision and coagulation. The number of cases is too small to permit purposeful comparison of results between the radiated and nonradiated tumors. In one of the cases of longest survival, No. 3, radiation was employed. In 3 cases of death since operation, radiation was also employed.

A notable occurrence was wound dehiscence in 3 cases. It seems reasonable to attribute this to the disturbance of circulation made by the cava ligation. In all of these cases resuture of the wound with wire stay sutures was followed by healing and recovery. The experience indicates that in all cases of cava ligation, wound closure should be made with stay sutures.

In none of the cases was there history of lower extremity thrombophlebitis prior to operation. Following the cava ligation there was temporary edema of the lower extremities in most cases. This largely disappeared postoperatively and is not a serious consideration which would not be the case had there been thrombophlebitis prior to operation.

#### COMMENT

Total cystectomy for carcinoma of the bladder has not increased the percentage of permanent cures. Ureterosigmoidostomy leaves many of the patients "electrolytic invalids." Cutaneous ureterostomy avoids electrolytic imbalance, but is of itself a considerable affliction.

The number of cures of deeply infiltrating bladder carcinoma by all surgical methods heretofore employed is discouragingly small. The same is true of radiation treatment. Evidence is accumulating which indicates that the percentage of cures by total cystectomy is no higher than by less radical procedures and indeed may be lower. Colby and Kerr<sup>2</sup> compared the results of cystectomy with those obtained by other less radical methods. In 82 cases of tumors of this sort, treated by means other than cystectomy, there were 9 five year survivors or 11 per cent. In 25 cases treated by total cystectomy, there were 2 survivors or 8 per cent.

Jewett<sup>1</sup> reports that only 2 of 61 patients (3.3 per cent) with deeply infiltrating bladder tumors treated either by total cystectomy or segmental resection survived five years. There was one survival among 13 cases in group B<sub>2</sub> and one survival among 48 cases in group C.

It may be presumed that the tumors covered by Jewett's report were more vicious than those covered by the Colby and Kerr report. It is impossible to know from such reports just what may have been the exact character of the tumors

<sup>2</sup> Colby, F. H. and Kerr, W. S., Jr.: Carcinoma of bladder: Evaluation of total cystectomy and other methods of treatment. *New Eng. J. Med.*, 244: 504-506, 1951.

with which they are concerned. It may be said that in a general way the results reported in these two papers are representative of general experience in dealing with bad bladder tumors; the comparatively bad and the very bad.

Results of extirpation operations are not available. They will contain a much higher operative mortality and morbidity than goes with the procedure here described. So-called "artificial bladders" made with segments of bowel have not avoided electrolyte imbalance, and from the standpoint of tumor extirpation are, of course, subject to the same faults as cystectomy with ureterosigmoidostomy.

The most desirable surgical treatment of infiltrating carcinoma of the bladder should eradicate the neoplasm and preserve normal bladder function as nearly as possible.

Vena cava ligation is not new. Some of the earliest ligations were made incident to its injury during nephrectomy. Pleasants,<sup>3</sup> in a lengthy review of 8 cases of caval ligation or excision made previous to 1911, stated that death resulted in only two of the patients. Vena cava ligation is now commonplace in the modern treatment of thrombo-embolic disease.

The truly massive electrocoagulation permitted by cava ligation accomplishes much more than can be accomplished by any form of extirpation presently feasible by dissection, and at the same time preserves vesical function— which is lost by cystectomy. The results obtained by the method described are encouraging in these cases of heretofore practically inoperable neoplasm.

#### SUMMARY

A method of surgical treatment of deeply infiltrating, extensive and malignant bladder tumors by massive electrocoagulation combined with ligation of the vena cava as a prophylactic measure to prevent pulmonary embolism is described.

The results to date in 10 cases of such neoplasms subjected to this form of treatment are described.

#### PURPOSE AND CONCLUSION

The purpose of this pre-entation rests upon the character of the neoplasm in these ten cases. All of them were of the most vicious sort. In none of them, subjected to former methods of operation, would there have been prospect of anything but fatal outcome within a year or so. The number of cases and duration of time since operation are entirely too limited to warrant a secure appraisal. A long period of time would be required for us alone to accomplish that and even then conclusions would be based on a not convincing number of cases.

We present at this time a new departure, and possibly a new hope, in this most disillusioning field of urologic effort for the purpose of prompting others to put it to trial to the end that with the least possible delay its merit may be accurately appraised by large experience.

228 Lowry Bldg., St. Paul, Minn. (F.E.B.F.; E.J.R.)

Union Central Bldg., Cincinnati, O. (W.P.M.)

Savannah, Ga. (J.V.)

<sup>3</sup> Pleasants, J. H.: Obstruction of inferior vena cava with a report of eighteen cases. *Johns Hop. Hosp Rep*, 16: 363-548, 1911

## CARCINOMA OF THE BLADDER: REVIEW OF 104 CASES FROM 1942 TO 1952

CHARLES PIERRE MATHÉ AND MIGUEL ANGEL LLANOS

*From the Department of Urology, St. Mary's Hospital, San Francisco, Calif.*

Urologists who deal with cancer of the bladder are appalled at the fatal outcome of the disease. This, in spite of improvement in the techniques for endoscopic removal, loop electrode excision through the open bladder, regional resection and cystectomy, combined with the use of palliative measures: administration of hormones and radiation therapy. Recent observations have confirmed the fact that fixation of the bladder due to invasion of the wall is a valuable criterion as to prognosis—indeed of greater prognostic significance than the size, location or grade of tumor malignancy. There seems to be a definite relation between urinary retention and the spread of bladder cancer; therefore, when vesical neck obstruction is encountered, it should be corrected at once. We should educate the laity as to the possible connection between hematuria and carcinoma of the bladder, and continue to impress upon the general profession the importance of a cystoscopic examination when hematuria is encountered, as all bladder tumors can readily be diagnosed by cystoscopy even in their earliest stages.

The advantage of cystectomy, with diversion of the urinary stream by uretero-sigmoidostomy or cutaneous ureterostomy, has not been evaluated. Although improvement of technique has lowered the mortality rate, the greater majority of patients who survive, die either of the effects of the operation (renal stasis, infection and uremia, or suffer from electrolyte imbalance with subsequent acidosis) or recurrence of cancer. The radical operation of exenteration consisting of block removal of the organs within the pelvis, along with the bladder is a drastic procedure that carries a high mortality rate and certainly is not acceptable to many patients.

This report consists of a review of 104 patients treated at St. Mary's Hospital between 1942 and 1952.

### CASE REPORT

Mr. M. K. (cook, age 68, case No. 16952) entered St. Mary's Hospital on May 14, 1951, complaining of dull left lumbar pain and urinary frequency of 3 weeks' duration. Dr. Stephen Erlach, the referring physician, had encountered blood and tumor cells in the urine, suspected bladder or prostatic cancer and sent the patient to us for diagnosis and treatment.

Laboratory findings were essentially normal except that the urine contained albumin, erythrocytes and leukocytes; blood examination within normal limits, and the Wassermann test negative. Cystoscopy on May 15 revealed a large, sessile, nodular, necrotic mass involving the right base of the bladder. An obstructing prostate and nodules of tumor tissue were seen on all four quadrants

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 22, 1952.

of the vesical neck. Cystography confirmed these findings. Bimanual palpation, under anesthesia, revealed fixation of the hard rubbery mass, involving the pelvic lymph nodes with extension into the prostate gland. A large, hard, retro-

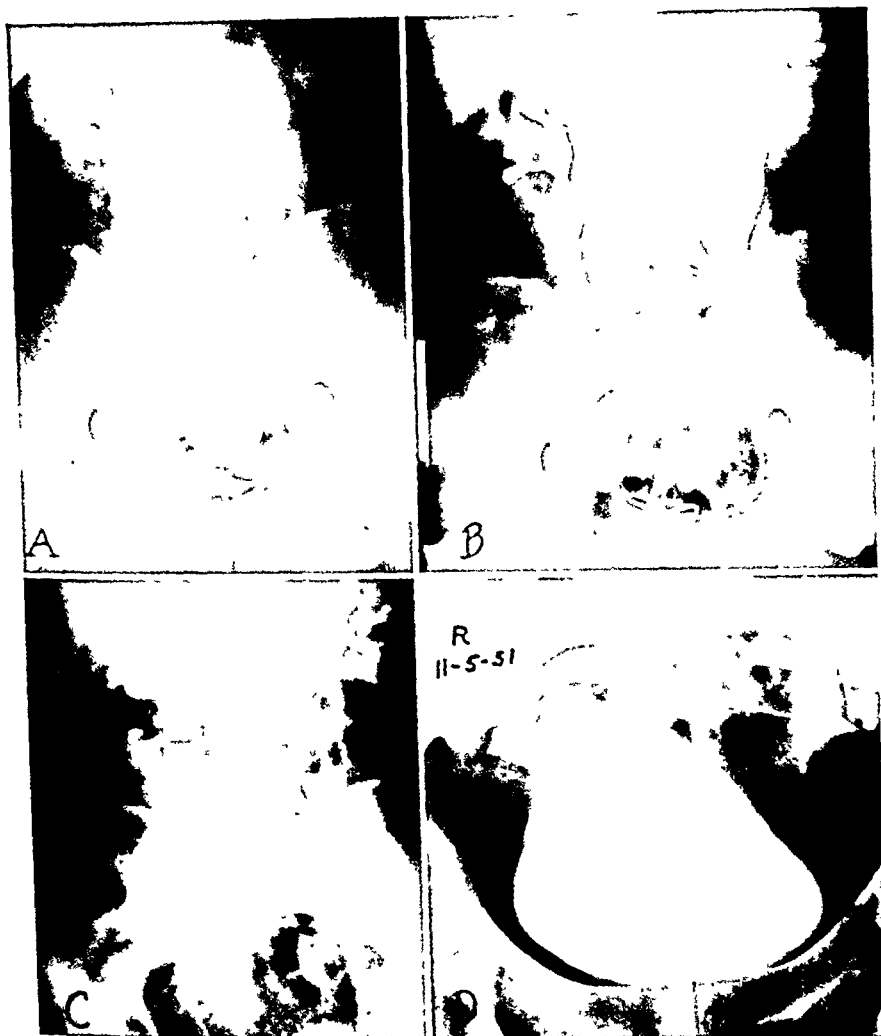


FIG. 1. *A*, retrograde ureteropyelogram and cystogram revealing filling defect in base of bladder due to fixed, advanced adenocarcinoma. *B*, retrograde ureteropyelogram showing marked displacement to midline of lower right ureter due to large metastatic retroperitoneal lymph node 12 by 5 cm. *C*, recheck retrograde ureteropyelogram showing midportion of right ureter no longer displaced, due to disappearance of metastatic node following radiation therapy (4050r). *D*, retrograde cystogram revealing normal bladder contour following treatment.

peritoneal, oval-shaped, fixed lymph gland, 12 by 5 cm., was palpated in the right lower abdomen. Retrograde ureteropyelography revealed that it had displaced the ureter to midline (fig. 1, *A* and *B*). An x-ray of chest and osseous system was negative for metastases. We realized that we were dealing with advanced



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The patient has gained 13 pounds in weight, is symptom free, and his urine no longer contains blood cells. Periodic 3-month physical examination, including cystoscopy, revealed no recurrence of cancer.

#### DIAGNOSIS

During the past 10 years, 25 per cent of the 101 cases seen were in the last stages of cancer, at which time current treatment was of little avail. Although excretory urography may reveal the advanced case, cystoscopy is the best method for the detection of early cancer, as it not only establishes the presence of cancer, but gives an idea as to the type of tumor, its size and location, degree of malignancy, and is an index as to treatment to be employed. The detection of malignant cells in the urine (Papanicolaou) is of great importance in diagnosis; however, the absence of cancer cells in the urine does not rule out bladder carcinoma.

Jewett and Strong have shown that the depth of penetration of the muscle wall is a most valuable prognostic sign of potential curability; more important than size, type and location of bladder cancer, or degree of malignancy revealed by histological study. Infiltration of the bladder wall is determined in carrying out bimanual examination, best under anesthesia, by which the hard, fixed rubbery mass is palpated. Cibert and Berben point out that it must not be confused with induration secondary to inflammatory processes of the bladder.

In tumors situated near the ureteral orifice, careful intravenous and retrograde ureteropyelography should be made to rule out origin in the kidney or ureter.

#### TREATMENT

In treating tumors of the bladder every patient presents an individual problem and the procedure depends upon whether the tumor is situated in the fixed base or in the distensible sphere making up the second and third bladder zones.

The pedunculated papilloma, with its characteristic fronds, although frequently benign, responds readily to endoscopic fulguration, but confirming biopsy should be carried out. As these are potentially malignant, it behooves one to take proper measures to prevent recurrence. The sessile mass, presenting central necrosis, is rather characteristic of malignant growth. It is interesting to note that the inflammatory polyp, commonly seen in the vesical neck and posterior urethra, unlike polypi of the lower bowel, do not undergo cancerous degeneration.

We favor transurethral resection for the early tumor when it is situated on the fixed base or posterior wall of the bladder. In removing the tumor it is well to include 1.5 cm. of healthy surrounding bladder mucosa and thoroughly destroy the base by extensive electrocoagulation (16 cases). Larger infiltrating tumors, situated on the lateral, anterior and posterior wall in the second and third bladder zones including the fundus, i.e., the distensible portion of the bladder, are best treated by regional resection including the entire bladder wall and 2.5 cm. of surrounding healthy tissue (6 cases).

Vesical papillomatosis has been thought to be due to virus infection. We advocate the liberal use of phenol, glycerine and alcohol at the end of open operation

carcinoma infiltrating the bladder wall, and elected to carry out endoscopic resection, hormone and radiotherapy.

On May 23, the sessile mass, weighing 8 gm., was removed, including 1.5 cm. of healthy surrounding tissue, and the base thoroughly fulgurated. Histologic study revealed adenocarcinoma (fig. 2, *A*). The patient was placed on daily doses of 25 mg. of diethylstilbestrol. Dr. Charles Capp administered two courses of deep x-ray therapy: 2100r (air), size portals 20 by 20 cm., over the right

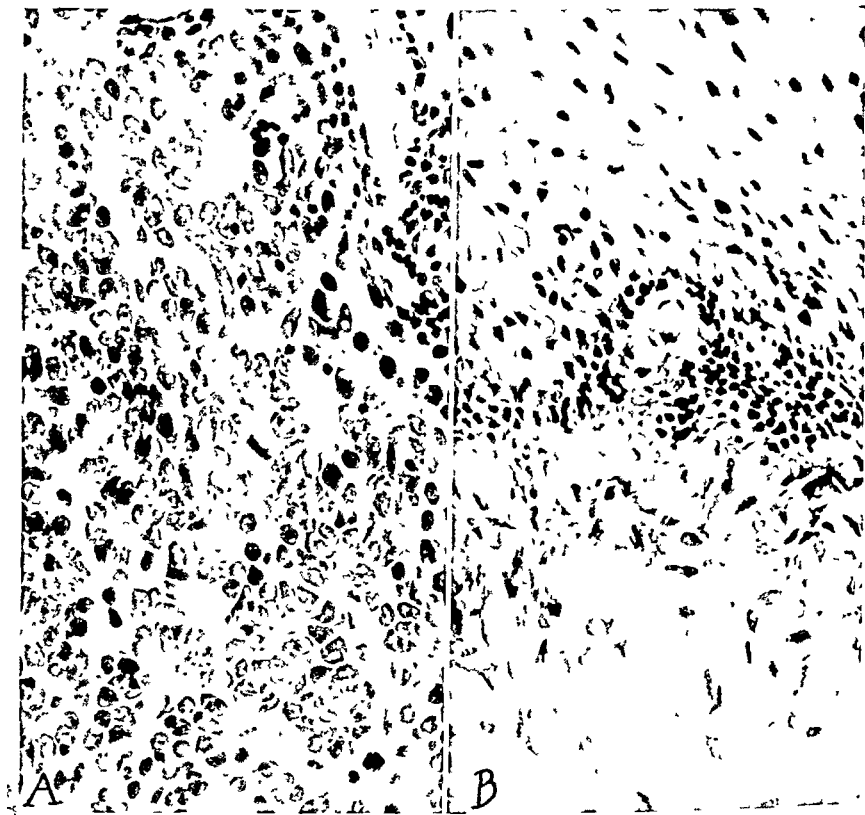


FIG. 2 *A*, photomicrograph of bladder tumor showing polypoid adenocarcinoma, quite cellular, with definite glandular pattern (grade 2 malignancy). *B*, section of small, sessile area on vesical neck removed 6 months after treatment. Note low grade inflammatory changes of bladder tissue covered with squamous epithelium, but no evidence of malignancy.

abdomen, and 1950r (air) over posterior right pelvis, from May 28 to August 10, with one month intermission.

The indurated areas in the pelvis associated with the prostate, and the large retroperitoneal lymph node disappeared, and 6 months later recheck ureteropyelography showed that the mid-portion of the right ureter was no longer displaced, and cystography revealed normal bladder contour (fig. 1, *C* and *D*). A small sessile area on the right anterior quadrant was resected on November 1, and histologic study revealed low-grade inflammatory changes of the tissue covered with squamous epithelium, but no evidence of malignancy (fig. 2, *B*).

and Borzone are of the opinion that trauma following mechanical action due to compensatory muscular effort to evacuate retained bladder urine lowers resistance to carcinogenic factors, thereby activating a latent predisposition to the formation of cancer.

*Radiation therapy.* We prefer radiation therapy as an adjunct to surgical or transurethral removal, and have used radiation prior to partial cystectomy in order to seal lymphatic channels, thereby lessening the danger of spreading cancer cells during manipulation at time of operation.

It is of particular value in the treatment of papillomatosis, papillary carcinoma, and questionable in dealing with leiomyosarcoma and epidermoid carcinoma. Costolow reported 24 cases of papillary type of tumor, of which 33 per cent survived 5 years after treatment.

In 2 of 24 cases treated by radiation therapy, radium was inserted through the open bladder. We did not use radon seeds or radioactive isotopes. Following x-ray therapy the unpleasant sequelae of cystitis seem to be less. The observations of Holmes, et al., in the use of supervoltage, 1,000,000 kilovoltage, in bladder cancer offers some promise.

*Hormone therapy.* Shortly after 1942, when orchiectomy and stilbestrol therapy were successfully used as an additional means in combating prostatic cancer, it was applied in the treatment of malignant tumors of the bladder.

In our series of 104 cases, bilateral orchiectomy had little effect in the amelioration of 2 hopeless advanced cases of bladder carcinoma. We now include the use of estrogen therapy as an adjunct to surgical removal, giving 25 mg. stilbestrol daily. We have found it to be of particular value in tumors situated near the vesical neck in the male.

#### ANALYSIS OF CASES

In review of our 104 cases, 80 per cent of the patients were between the fifth and seventh decades of life, the youngest being 37 and the oldest 82; 67 males and 37 females.

Sixty-nine of these patients presented papillary growth of which 18 were benign papilloma, 33 papillary carcinoma, 17 transitional cell papillary carcinoma, and 2 papillomatosis. We have treated numerous polyps of the bladder, and have never observed them to become malignant.

Of particular interest is Mrs. B. F. (aet 60, case No. 892112), repeatedly relieved of recurrent papilloma by fulguration, in whom highly malignant papillary carcinoma developed 10 years later, to which she succumbed, substantiating the theory that recurrent papilloma is often of higher malignancy than the original growth. Mrs. C. C. (aet 75, case No. 21675) was successfully relieved of papillary carcinoma of the fundus of the bladder in 1944, and 5 years later, in making the periodic check-up, two small white nodules were noted, which proved to be malacoplakia rather than original growth.

Thirty-one cases of carcinoma were encountered: 7 transitional cell, 3 epidermoid, 3 squamous cell, 18 adenocarcinoma. In 3 cases adenocarcinoma was secondary to carcinoma of the sigmoid and 2 succumbed within a year. There

in order to prevent the spread of cancer cells (Kirwin). We have not used podophyllin in the treatment of papillary tumors.

When the tumor involves the ureteral orifice, the ureter is transplanted in an adjacent portion of the bladder wall. This was successfully carried out in a case (No. 164726), and the patient is living and well after 7 years with no evidence of recurrence of papillary carcinoma and no sign of renal stasis.

Another patient (No. 152292) underwent regional resection for papillary carcinoma with extensive involvement of the left lower bladder wall. The sclerosis that took place in healing following operation, obliterated the lower ureter, resulting in stasis and consequent abscess formation of the kidney. This was relieved by nephro-ureterectomy. When the lower ureter is involved and when the kidney is destroyed by back pressure, or an infectious process, we do not hesitate to carry out complete nephro-ureterectomy.

In dealing with infiltrating tumors near the vesical neck we have used trans-urethral resection with extensive electrocoagulation of the base. In recent years the mortality rate of total cystectomy has been lowered due to improvement in technique and the liberal use of blood transfusion. Thus, the debilitated elderly patient, usually in the sixth and seventh decades of life, has a more reasonable chance of surviving. (Leadbetter, Marshall, Thomas.) Improvement in the technique of uretero-intestinal anastomosis, including careful approximation of the mucosa of the ureter to that of the bowel, has lowered the incidence of stricture formation at site of implant. We thus prevent subsequent dilatation of the ureter and kidney pelvis, which often produced stasis, resulting in infection and uremia. In patients presenting greater risk, diversion of the urinary stream is made by cutaneous ureterostomy.

In a recent personal communication, Kirwin stated: "My only advice is not to avail yourself of this terrific operation of transplantation of the ureters, cystectomies, prostatectomies and vesiculectomies which are herculean tasks. If the patient can stand it he usually gets well, but his life is shortened considerably. As these people are usually between 65 and 75 years of age, and not good operative risks, it is a formidable undertaking." McCarthy believes that the general run of vesical tumors are amenable to conservative or semi-radical treatment and he is surprised that there is a tendency to suppress all methods less radical than cystectomy.

One must realize that we are dealing with patients in the latter decades of life and many are poor risks for the extensive intervention of cystectomy with an operative mortality rate varying from 11 to 27 per cent. The greater percentage of those who survive die either from later effects of the operation, i.e., acidosis, infection, urinary stasis, uremia, etc., or from recurrence of cancer.

We have observed 7 cases in which there was no recurrence of tumor after the removal of bladder neck obstruction.

We now make it a practice, meticulously, to relieve concomitant vesical neck obstruction early, as we believe that there is less recurrence of bladder cancer following this procedure. Apparently, the back pressure resulting from stasis favors the action of carcinogenic urine substances on bladder mucosa. Trabucco

nodes following transurethral resection, correction of bladder neck obstruction, radiation and hormone therapy.

The cystoscopic picture is still the most accurate guide in diagnosis and treatment. Cystography is a valuable aid in localizing the larger growths in the distensible portion of the bladder.

Extent of infiltration of the bladder wall, and the amount of necrosis, are the most valuable prognostic signs. One must not confuse fixation resulting from inflammatory disease with that due to cancer.

We emphasize the importance of early correction of concomitant vesical neck obstruction as recurrence of tumor is less following this procedure. We advocate the more general use of radiation therapy, not only as an adjunct to surgical or transurethral removal, but also preoperatively, before open operation, to prevent spread of cancer through the lymphatics.

*450 Sutter St., San Francisco 8, Calif.*

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were 4 less common tumors noted: hemangioma 1; leiomyosarcoma 1; and malacoplakia 2. All cases of epidermoid type of carcinoma, as well as that of leiomyosarcoma had infiltrated the bladder wall when first seen, and succumbed within 2 years.

Forty were treated by cystoscopic fulguration, 16 by transurethral resection and extensive fulguration of base of tumor, 24 by electric loop resection through the open bladder, 3 by fulguration through open bladder, 2 by implantation of radium through the open bladder, 6 by segmental resection, and 5 by cystectomy including ureterosigmoidostomy, 1 including radical prostatectomy and seminal vesiculectomy. In 9, the disease was so far advanced that palliative measures were employed: cystectomy in 2, bilateral cutaneous ureterostomy in 1, bilateral orchiectomy 2, catheter drainage 1, radiation therapy 1, and no treatment 2. Unfortunately, these patients were in the last stages of cancer and nothing was achieved except to allay suffering and prolong life for a short time.

In 6, complete ureteronephrectomy was performed either for obstructive infected hydronephrosis or an involvement of the lower ureter by cancer.

Nineteen of the 104 cases succumbed postoperatively, or within a few months after leaving the hospital. These were desperately ill patients in advanced stage in which heroic methods were carried out too late. Two succumbed after total cystectomy and ureterosigmoidostomy, 1 after cystoscopic fulguration, 7 after removal through the open bladder, in addition to the 9 patients, noted above, in whom the palliative measures were employed. Of interest is one patient who died from cerebral metastases of transitional cell carcinoma. Patients presenting extensive necrosis and fixation due to infiltration of the bladder wall, revealed at bimanual examination, had a poor prognosis. The greater majority of these cases succumbed shortly after treatment.

In contrast were the 15 cases in which meticulous surveillance was carried out: examination of the urine for blood and cystoscopy every 3 to 12 months, enabling us to immediately attack recurrent lesions and add radiation and hormone therapy.

The survival in these was: 1 case, 15 years; 2 cases, 14 years; 1 case, 8 years; 2 cases, 7 years; 2 cases, 3 years; 3 cases, 1 year; 2 cases died 3 and 5 years later from other causes—no recurrence of cancer; 1 case died 1 year later from leiomyosarcoma; 1 case died 4 years later from papillary carcinoma.

#### SUMMARY

One hundred and four cases of carcinoma of the bladder, treated between 1942 and 1952, are reviewed.

The high mortality rate (18.2 per cent) is due to the fact that in the majority of these cases we were dealing with desperately ill patients in the last stages of the disease. The survival rate was greater among those patients seen earlier, whose treatment was augmented by relief of bladder neck obstruction, radiation and hormone therapy; and also, by surveillance at regular intervals.

A case is presented in which there was remarkable regression of advanced bladder cancer as well as disappearance of metastatic retroperitoneal lymph

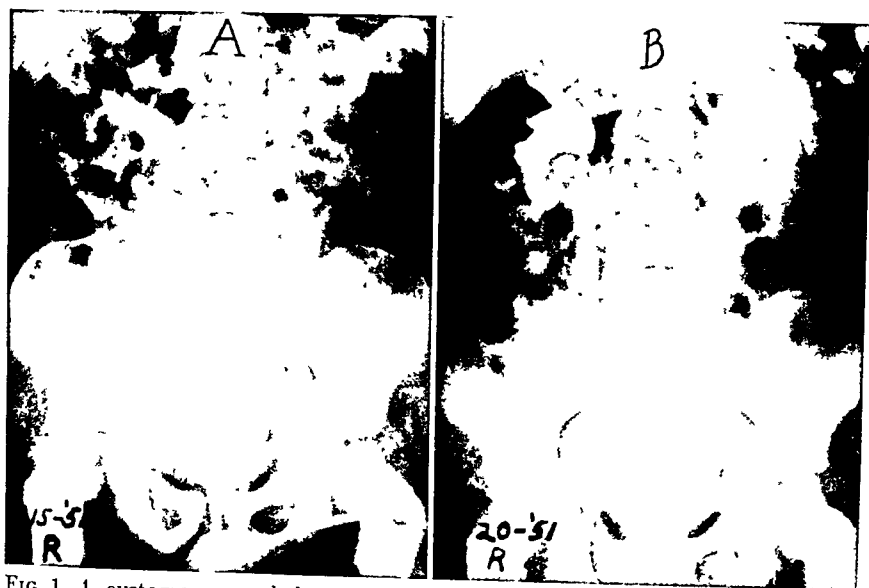


FIG. 1. *A*, cystogram reveals large filling defect in bladder. *B*, excretory urogram prior to surgery reveals increase in size of bladder filling defect with early obstruction of right ureter.

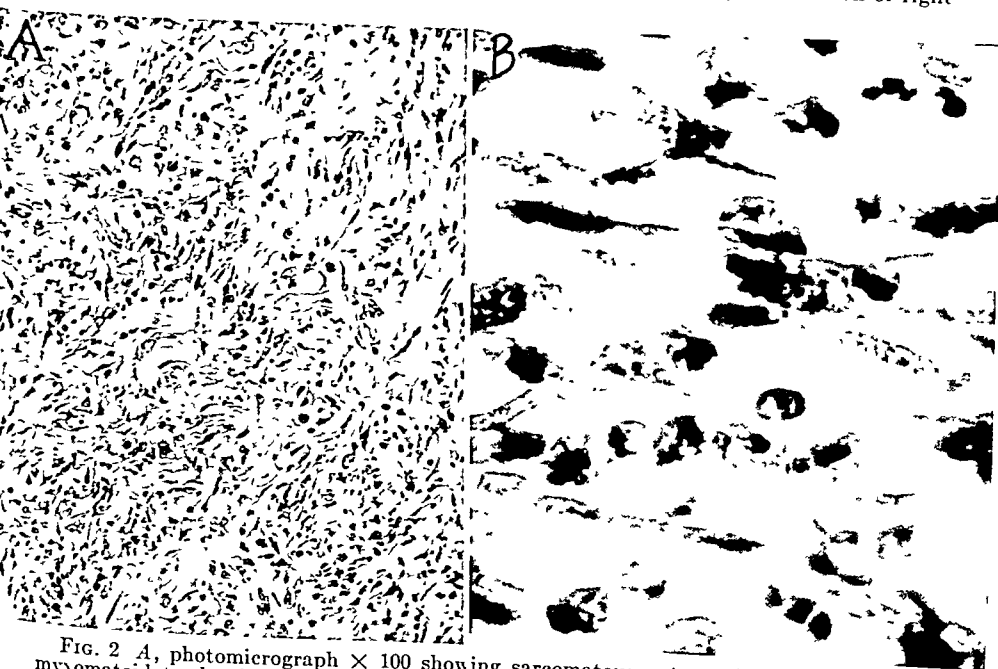


FIG. 2. *A*, photomicrograph  $\times 100$  showing sarcomatous nature of lesion, with some myxomatoid tendencies. *B*, photomicrograph  $\times 440$ . Note immature muscle fibers and tumor giant cell.

cytoplasm which appears basophilic. The cytoplasm is frequently drawn out into streamer tails. The nuclei are moderately chromatic in many places and almost clear in others. Many cells show no distinct cytoplasmic component. Numerous mitotic figures are seen in some areas. Much of the tumor is superficial to the



# RHABDOMYOSARCOMA OF THE BLADDER: REVIEW AND REPORT OF A CASE

HERMAN I. RIDDELL AND HAROLD G. KUDISH

*From the Department of Urology, Childrens Hospital, Los Angeles, Calif.*

Rhabdomyosarcoma is among the most infrequently occurring tumors of the bladder. Except for osteogenic sarcoma and chondrosarcoma, it is the rarest tumor to be found in this organ. The confusion which exists in the literature relative to histopathologic classification makes it difficult to ascertain the true incidence of this entity. Some of the more undifferentiated tumors described as round or spindle cell sarcomata may represent rhabdomyosarcoma.

In a comprehensive review of the literature, Crane and Tremblay reported 151 various types of bladder sarcomata up to 1943. Kretschmer, in 1947, documented only 15 cases of rhabdomyosarcoma from the literature, to which he added his own case. Since that time four additional cases have been reported. The rarity of this tumor has prompted us to report a recent case of rhabdomyosarcoma of the bladder which we believe to be the twenty-first case in the literature.

## CASE REPORT

D. H. No. 51936, was a white male infant, aged 26 months, first seen at Childrens Hospital in May 1951. Two months earlier he sustained a minor blow to the suprapubic region. Painless hematuria recurring at intervals was noted. Cessation of gross hematuria was followed by persistent microscopic hematuria. An excretory urogram done elsewhere was normal. Physical examination was entirely normal, the only positive finding being erythrocytes in the urine. Cystoscopic examination revealed a large, lobulated, grayish-white mass in the anterior vertex of the bladder. Visualization was difficult but it appeared to be old thrombus. Cystogram (fig. 1, A) revealed a large filling defect corresponding to the mass seen at cystoscopy. On the assumption that the mass was old thrombus, the bladder was irrigated with 5 per cent Caroid solution for 3 days. A repeat cystogram was unchanged. Three months following the original injury cystotomy was done. The bladder was filled with grape-like, yellow, gelatinous masses. A large, pedunculated, firm, smooth mass occupied the right base of the bladder near the trigone. Several biopsies were taken. The postoperative course was uneventful. Biopsy slides were sent to the Armed Forces Institute of Pathology where a diagnosis of rhabdomyosarcoma of the bladder was confirmed. Lack of co-operation on the part of the parents considerably delayed definitive surgery. During this interval of 7 weeks the tumor had grown out of the cystotomy wound in a fungating mass. Excretory urography revealed development of slight ureterectasis and pyelectasis on the right with increase in the size of the filling defect in the bladder (fig. 1, B). On August 16, 1951, total cystectomy, pelvic lymphadenectomy, and ureterosigmoidostomy were performed. The microscopic report by Dr. John Schaefer was as follows (fig. 2): "The tumor cells are characterized in many areas by moderately enlarged, elongated nuclei, together with abundant

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 21, 1952.

The gross pathological appearance of rhabdomyosarcoma does not differ appreciably from the other non-epithelial bladder tumors. The growth usually occurs in grape-like clusters, being likened in appearance to hydatidiform mole. The surface of the tumor is smooth and translucent, the color generally being white to grayish yellow. The consistency is rather gelatinous. Ulceration of the overlying mucosa may be present.

TABLE 1. *Rhabdomyosarcoma of the bladder reported in the literature*

| AUTHOR                            | SEX | AGE     | LOCATION                                      | RESULT        |
|-----------------------------------|-----|---------|-----------------------------------------------|---------------|
| Monckeberg 1907                   | F   | 23      | Posterior bladder wall                        | Death         |
| MacKenzie & Chubb 1928            | F   | 69      | Floor of bladder and trigone                  | Death         |
| Houette 1929                      | M   | 13 mo   | In congenital diverticulum                    | Death         |
| White 1929 (cited by Kretschmer)  | ?   | 22 mo   | Anterior wall of bladder                      | Post          |
| Monseriat 1933                    | M   | 13      | Right wall of bladder                         | Death         |
| Welfeld, Hill & Hillebrand 1936   | F   | Infant  | Not stated                                    | Death         |
| Idem                              | M   | 2       | Anterior bladder wall                         | Death         |
| Vermoten 1939                     | F   | 20 mo   | Trigone                                       | Death         |
| Ratliff & Valk 1939               | M   | 6       | Entire bladder                                | Death         |
| Idem                              | M   | 65      | New left ureteral orifice attached to pedicle | Death         |
| Uhlmann, Grossman and Calvin 1939 | M   | 10 mo   | Wall of bladder                               | Death         |
| Hunt 1943                         | M   | Newborn | Floor of bladder                              | Death         |
| Idem                              | M   | 2 plus  | Entire bladder                                | Death         |
| Khoury and Speer 1944             | M   | Infant  | Trigone                                       | Death         |
| Hirsch & Gasser 1944              | M   | 5       | Extramural retrocervical                      | Death         |
| Kretschmer 1947                   | M   | 53      | Dome of bladder                               | Alive 4 years |
| Meinel, Heath & Miller 1944       | M   | 32      | Left lateral wall by pedicle                  | Free of tumor |
| Minschin 1947                     | M   | 17 mo   | Vesical orifice by pedicle                    | Death 7 mo.   |
| Vipond 1948                       | M   | 21 mo   | Posterior bladder wall                        | Death 5 mo    |
| Foster & Lund 1951                | M   | 10 mo   | Bladder neck and post urethra                 | Death 18 mo   |

Histologically the pathognomonic cell is the immature or mature striated muscle fiber showing definite myofibrillae with or without cross striations. These fibrillae are best demonstrated by the phospho-tungstic acid stain. Tumor giant cells are nearly always present and indicate the degree of anaplasia. These tumors do not metastasize to distant organs, but rather tend to invade the adjacent pelvic structures by direct extension.

Houette and others accept the hypothesis of Wilms who considers rhabdomyosarcoma an embryonal heterotopia due to an anomaly in development of the wolffian duct. Uhlmann, Grossman, and Calvin further expand this hypothesis by stating that cells of the myotome, the anlage of the striated muscle of the abdominal wall, may become displaced during the caudal growth of the

muscularis layer, however, areas of invasion of the muscle are noted. In some areas considerable space exists between individual tumor cells due to the myxomatoid tendencies of some portions of this lesion. A few large giant cells are seen; no cross striations are noted in the muscle cells. The tumor has distinct polypoid and myxomatous qualities. Three of the pelvic lymph nodes contain tumor, but sections of the prostate show no tumor."

The patient tolerated surgery very well. Hypopotassemia developed on the fifth day, as demonstrated by electrocardiogram and serum levels, but this was promptly corrected by parenteral administration of potassium chloride. Acidosis was not a problem following surgery. Radiation therapy was started on the twentieth day postoperatively and a total of 2400r was given. The patient was discharged to the Out-patient Department with all wounds healed.

Follow-up studies revealed normal blood chemistry on repeated examinations. Excretory urography revealed slight pyelectasis on the right with normal silhouette on the left. On January 15, 1952, the patient was well so far as examination could determine. One week later, however, re-admission was necessary because of marked ascites. Paracentesis resulted in the removal of 3120 cc of hazy, straw colored fluid. Radio-active chromic phosphate, in a dose of 4.3 millicuries, was introduced into the peritoneal cavity to inhibit the development of ascites and make the patient more comfortable. One month later the ascites had not recurred. At the time of this report, ascites has returned and the child's condition is deteriorating rapidly.

#### DISCUSSION

The contrasting incidence of sarcoma and carcinoma in early life is striking. Pack and LaFevre found sarcoma to be 22 times as frequent as carcinoma in patients under 25 years of age. If all ages are included, the incidence of carcinoma is nearly 9 times that of sarcoma. Campbell states that there is no authenticated case of carcinoma in the very young. From the abstract of cases previously reported (table 1), it is apparent that rhabdomyosarcoma is predominantly seen in males in the approximate ratio of 4:1. This ratio coincides with the incidence noted in the entire group of bladder sarcoma reported by others. Significantly, 15 cases occurred in patients under the age of 10 years with 12 cases actually under 2 years of age. The remaining cases occurred one in each decade from age 23 to age 69.

The classical triad of suprapubic pain, hematuria, and disturbances in micturition was the symptomatology most frequently associated with rhabdomyosarcoma of the bladder. Descalopoulous found hematuria to be an infrequent presenting symptom. However, in the majority of cases it is noted during some period of the disease. A palpable suprapubic mass which fails to disappear following catheterization is of further diagnostic value. Excretory urogram or cystogram may reveal the typical filling defect in the bladder. With extension of the tumor mass and encroachment on the ureters, hydronephrosis and hydro-ureter may appear. Deming's case in 1924 was the first to be diagnosed by cystoscopy. Because of the classical gross appearance of the tumor, cystoscopy should suggest the diagnosis of sarcoma.

## WHAT MAKES THE PROSTATE GROW

WILLIAM WALLACE SCOTT

*From the James Buchanan Brady Urological Institute, the Johns Hopkins Hospital,  
Baltimore, Md.*

It is a great privilege and pleasure to be here at the meeting of the Western Section, and first I wish to thank those responsible for my invitation. Having familiarized myself with the list of distinguished men who have preceded me as Robert V. Day lecturers, I approach my assignment with considerable apprehension and humility.

My age prevented me from knowing Dr. Robert Verne Day, chemist, surgeon, urologist, professor and past president of the Western Section, whose untimely death occurred on April 30, 1939. Yet from what I can deduce from his biography and writings, I am sure that association with him would have been most pleasurable and profitable to me, particularly profitable in ideas concerning the mechanisms of action of the male sex hormones.

You of the Western Section will recall that the last article he wrote for the *Journal of Urology* and which appeared therein in the February 1939 issue was entitled "Male Sex Hormone Therapy."<sup>1</sup> In spite of the expenditure of large sums of money and the time and effort of many, few truths have been added to what he wrote then. In spite of leads which were inviting and results which were encouraging he wisely recognized that, "Hormone therapy is in no sense to be considered a substitute for surgical relief in major prostatic obstructions, [and] in true hypertrophy, it is a mistake to resort to any type of surgical relief until the so-called false capsule is well formed, that is to say, until it is ripe, so to speak, just as we remark in speaking of cataract. The reason for this, when a premature enucleation is performed, is that a ragged prostatic bed is left, and prolonged or permanent post-operative urinary irritation [or recurrence] ensues. If, on the other hand, transurethral resection is performed, the residual prostate is eventually almost sure to undergo marked hypertrophy and necessitate further surgical relief. The so-called prophylactic resection is a misnomer, is evidence of bad surgical judgment and approximates the supreme error." We would do well to recall these principles today.

His optimism was illustrated by the following: "Indeed it is risky to venture an opinion as to what will be the true field of male sex hormone therapy until the collective experience of clinicians and research scientists (over a period of perhaps 10 to 25 years) has filled many now empty gaps in our knowledge. Nevertheless, the present status of our knowledge warrants a prediction that its therapeutic potentialities are enormous in both men and women."

My subject is, "What Makes the Prostate Grow." To be consistent with the facts, the listing of the title should have included a question mark at the end.

The Robert V. Day Lecture read at annual meeting, Western Section, American Urological Association, Pasadena, Calif. May 20, 1952. Read in part at 1952 annual meeting of Mid-Atlantic Section, American Urological Association and at the 1952 annual meeting of American Association of Genito-Urinary Surgeons.

<sup>1</sup> Day, R. V.: *J. Urol.*, 41: 210, 1939.

wolffian duct to its vesico-urethral destination. Hunt and others feel it reasonable to believe that rhabdomyosarcoma may arise from the normally present striated muscle elements in the anterior aspect of the prostate and the sphincter of Henle. Based on a study of four museum specimens, Shattock was of the opinion that vagrant sarco blasts which had become displaced beyond their usual deeper limits into the subepithelial tissue of the bladder gave rise to rhabdomyomas. The latter two hypotheses, however, fail to explain the occurrence of rhabdomyosarcoma in the dome of the bladder as reported by both Kretschmer and Meisel, et al.

The prognosis with rhabdomyosarcoma of the bladder is extremely dismal as reflected by the results of treatment in the cases reported. All cases occurring in infants and children terminated fatally, the longest period of survival being 18 months from the time of diagnosis. Two cases in adults with the tumor confined to the dome of the bladder survived four years and seventeen months respectively following segmental resection of the bladder. The latter case revealed no evidence of tumor at autopsy following death from an unrelated cause.

The spread of this tumor is by direct extension rather than by distant blood borne metastases. It would appear, therefore, that early radical surgery offers the treatment of choice. With the continued improvement in technic of cystectomy and uretero-intestinal anastomosis, it is felt that earlier diagnosis will facilitate recovery by employment of these methods. Where the tumor occurs on the dome of the bladder, in the older age group, wide segmental resection appears to give satisfactory results.

#### SUMMARY

The twenty-first case of rhabdomyosarcoma of the bladder is reported. The clinical features, diagnosis and pathology are briefly discussed. The early diagnosis is stressed and early radical surgery is recommended.

*2010 Wilshire Blvd., Los Angeles, Calif. (H.I.R.)*

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300 gm. control rats, intact and fed normally, the prostate gland weighs some 600 mg. Five weeks after castration, rats of the same age, strain and weight and fed with the same food, group B, have prostates which weigh less than 50 mg. A profound atrophy has occurred, and histologically this atrophy includes both fibromuscular and epithelial elements.

Slide 2 [fig. 1<sup>4</sup>] prefaces slide 3 and shows a diagram of a prostatic fistula in the dog which permits a study of prostatic secretion, a function of the prostate. In slide 3 [fig. 4<sup>1</sup>] we see that castration virtually abolishes prostatic secretion even under parasympathetic stimulation. Histological studies of such castrate-fistula preparations show atrophy of all elements.

Let us ask ourselves the obvious question: What have we eliminated from the body when we have removed the testes? The answer is less obvious.

#### TESTICULAR HORMONES

Somewhat over 100 years ago Berthold,<sup>5</sup> on the basis of transplantation experiments in the cock, presented evidence that the testes exert decided effects on the organism through the blood stream independent of established nervous pathways. Since then, tremendous energy has been expended on determining the nature of the hormones elaborated by the testis, the cells responsible for their production and the physiological actions of the hormones produced.

Both crystalline androgens and estrogens have been extracted chemically from testicular tissue. This, however, does not necessarily mean that both are made in the testis nor in the form in which they were isolated. Several schools of thought exist currently with regard to the particular testicular cells responsible. Thus, one school presents evidence to support their belief that the interstitial cells of Leydig make both androgens and estrogens;<sup>6</sup> a second, that androgens are made by these same cells but estrogens are made by tubular cells, most likely the Sertoli cells;<sup>7</sup> a third, that whereas androgen is most likely made by Leydig cells, estrogen is formed outside the testis; a fourth, that the second hormone of the testis, although like estrogen, being water-soluble is not identical with it, and most likely is formed by the tubules.<sup>8</sup> This substance has been named "inhibin."

Several years ago our laboratory investigated certain aspects of this particular problem, and briefly the results were as follows: 1) Sertoli cell tumors in dogs produce estrogen, and 2) the lipid content of the Leydig cell and Sertoli cell changes with age.

First about the dog: Dr. Willard E. Goodwin,<sup>7</sup> formerly not only my right hand but my left, observed that certain testicular tumors in male dogs were associated with sudden and marked feminizing changes. These dogs developed breasts, abdominal pigmentation and became sexually attractive to other male dogs. Their prostates were large and on section showed marked squamous metaplasia. The breasts on section showed marked cystic hyperplasia similar to that

<sup>4</sup> Huggins, C., Masina, M. H., Eichelberger, L. and Wharton, J. D., *J. Exp. Med.*, 70: 543, 1939.

<sup>5</sup> Berthold, A. A. *Arch. f. Anat., Physiol. u. wissenschaft. Med.*, 1849, p. 42.

<sup>6</sup> Maddock, W. O. and Nelson, W. O., *J. Clin. Endocrinol.*, 11: 769, 1951.

<sup>7</sup> Berthrong, M., Goodwin, W. E. and Scott, W. W., *J. Clin. Endocrinol.*, 9: 579, 1949.

<sup>8</sup> McCullagh, D. R. and Walsh, E. L., *Endocrinol.*, 19: 466, 1935.

Understanding fully that we don't know precisely what makes the prostate grow, I shall endeavor to outline what might be considered the present status of the problem and, if time permits, indulge in a little biological extrapolation.

Most of the work which I shall report from our laboratory is principally the result of the efforts of our resident staff, my function being largely that of providing a modern mammalian laboratory in which to work. Most of the work has been done in animals, and almost all of it concerns the effects of endocrine manipulation on prostatic size, histology and function. All has been done with the thought that in order to understand abnormal prostatic growth in man we must first understand normal growth.

During the normal course of events placental male mammals are born with prostate glands. During the last trimester, and for a short time after birth, distinct histological changes can be observed which include squamous metaplasia and focal hyperplasia of fully differentiated epithelium. These changes occur at a time when changes also occur in the breast, uterus and vagina of females, and it has been suggested that these changes are due to the action of gonadal hormones, derived either from the mother or from the fetal gonads under the stimulus of maternal gonadotrophic hormones.

Shortly after birth retrogressive changes occur, and it is not until the testes begin to elaborate their hormones that we again note changes in the size, histology and function of the prostate gland.

Barring the occurrence of acute, subacute and chronic inflammation or the development of prostatic stones, few changes are usually observed during the next two score years and ten. Thereafter, nodular hyperplasia develops in most glands and carcinoma in many. To this author, with the evidence at hand, the best working hypothesis is that both benign hyperplasia and cancer of the prostate result from a disturbance of the ratio and quantity of androgens and estrogens in these older men.

Let us first examine the evidence for endocrine regulation of normal prostatic growth.

#### THE EFFECT OF CASTRATION

For centuries it has been known that castration, both in animals and man results in profound changes in male accessories. That genius and tireless experimenter, John Hunter,<sup>2</sup> seems to have been one of the first to succinctly describe the effects of castration on prostatic size and functional capacity. Describing his observations in the bull, he wrote: "The prostate gland, Cowper's glands and the glands along the urethra are in the perfect male large and pulpy, secreting a considerable quantity of slimy mucus which is salt to the taste; while in the castrate animal these are small, flabby, tough and ligamentous and have little secretion."

This observation has been confirmed repeatedly in man and in many species of animals. Two examples follow:

Slide 1 [based on data from table 1<sup>3</sup>] shows the prostatic weight response in young adult rats 5 weeks after castration. Referring to group A, we see that in

<sup>2</sup> Hunter, John: In collected works, edited by J. F. Palmer, London, 4: 31, 1786.

<sup>3</sup> Grayhack, J. T. and Scott, W. W.: Endocrinology, 48: 453, 1951.

300 gm. control rats, intact and fed normally, the prostate gland weighs some 600 mg. Five weeks after castration, rats of the same age, strain and weight and fed with the same food, group B, have prostates which weigh less than 50 mg. A profound atrophy has occurred, and histologically this atrophy includes both fibromuscular and epithelial elements.

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<sup>6</sup> Maddock, W. O. and Nelson, W. O.: *J. Clin. Endocrinol.*, **11**: 769, 1951.

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<sup>8</sup> McCullagh, D. R. and Walsh, E. L.: *Endocrinol.*, **19**: 466, 1935.



found in dogs experimentally given estrogen. Their urinary estrogens were high, and analysis of the tumors themselves showed increased estrogen content. On section these tumors were composed almost entirely of Sertoli cells, all sudanophilic. This caused us to wonder, as had others before us, if the Sertoli cell normally produced estrogen.

One year later my former associate, Dr. Kenneth M. Lynch, Jr.,<sup>9</sup> taking a similar tack, began to study the lipid distribution in the cells of the human testis at all ages. He found that only two types of testicular cell accepted the fat stain, oil-red-O; the Leydig cell and the Sertoli cell. Independently the two of us graded the amount of fat present in these cells in 168 testes from humans ranging in age from 2 months premature to 84 years. The results of these estimations revealed that from puberty to old age Leydig cell lipid falls off and Sertoli cell lipid increases. In an independent study by Sargent and McDonald,<sup>10</sup> the curve which they obtained when they plotted the number of Leydig cells per seminiferous tubule against age compared nicely with ours for Leydig cell lipid and age.

Of particular interest to us was the observation that no variation from the normal pattern was observed in either benign prostatic hyperplasia or cancer.

On the basis of this work, and the work in the dog, it is tempting to assign estrogen production to the Sertoli cells, and to postulate that, with age, estrogen production exceeds androgen production. However, the evidence is not conclusive. Furthermore, solution of the problem by present histologic techniques does not appear possible, for histochemists are not yet in a position to identify or localize the steroids of the testis.

Unfortunately then, the nature of the internal secretions of the testis remains in doubt and probably will until the steroid chemist turns his attention from the analysis of dead tissue to the analysis of testicular effluent blood. Until such a time as the nature of testicular hormones is determined, it is inaccurate to assign the effects of castration to only androgen withdrawal, as is commonly done.

#### THE PHARMACOLOGIC ACTION OF ANDROGENS AND ESTROGENS

This author has chosen to use the term pharmacologic rather than physiologic because, to date, rates of secretion of androgens or estrogens have not been defined. Initially, I wish to emphasize that the pharmacologic, physiologic or pathologic actions of androgens and estrogens depend on a multiplicity of conditions which include among many the size of the dose administered, whether administered singly or in combination and whether to an intact animal or a castrate, the condition of the liver and the organism as a whole and the state of nutrition. Furthermore, when we are talking of their effects on the prostate gland, we must describe them in terms of whether it is an effect on the size of the gland, its function and the histologic elements effected, whether fibromuscular or epithelial.

*Androgen administration.* Slide 4 [based on data from table 1<sup>3</sup>] shows that in the young adult rat the prostate weighs approximately 600 mg. (A). Five weeks

<sup>9</sup> Lynch, K. M. Jr. and Scott, W. W.: J. Urol., **64**: 767, 1950.

<sup>10</sup> Sargent, J. W. and McDonald, J. R.: Proc. Staff Meet., Mayo Clin., **23**: 249, 1948.

after castration it weighs approximately 50 mg. (B). If the castrate is given 0.4 mg. of testosterone propionate every other day for 2 weeks, the prostate may weigh 1100 mg. (D). Histologically one observes a uniform development of all the true prostate tissue in these androgen-treated castrates with no recognizable abnormal changes.

Slide 5 [fig. 5<sup>11</sup>] shows that in the immature dog, prepared according to the Huggins' technique previously illustrated, no secretion occurs. If one administers 25 mg. of testosterone propionate to the immature dog, within 1 week the prostate begins to secrete in response to pilocarpine and the gland increases in size. In the mature castrate [slide 6—fig. 6<sup>11</sup>] secretion is maintained as long as testosterone is given, in this case in pellet form. Other examples of androgen stimulation of prostatic growth could be given.

*Estrogen administration.* Great confusion arises as to the effect of estrogen on prostatic growth, and as stressed earlier, much of this confusion revolves around the size of the dose given and the particular portion of the prostate to which reference is made. As early as 1933, Lacassagne,<sup>12</sup> administering estrogen to mice for periods as long as 5 months, observed considerable growth of the dorsal prostatic lobes, leading to retention of urine and hydronephrosis. These initial observations were confirmed by many, including de Jongh,<sup>13</sup> Burrows and Kennaway,<sup>14</sup> David and his co-workers<sup>15</sup> and Korenchevsky and Dennison.<sup>16</sup> Subsequently, Burrows<sup>17</sup> showed that this growth was not limited to the dorsal lobes but extended to all the lobes of the prostate, effecting changes primarily in the fibromuscular components and to a lesser extent in the epithelial elements. It is interesting to note that Moore and Price<sup>18</sup> did not observe these striking changes presumably because of too low dosage and too brief periods of injection.

On the contrary, certain doses of either naturally occurring or synthetic estrogens will shrink the prostate glands of a mature rat and will cause cessation of prostatic secretion in the Huggins' fistula dog. Whether this action is a direct antagonistic one to testicular androgen or acts indirectly through the pituitary is as yet unsettled. Huggins believes it is a direct one and slide 20 [chart 3<sup>19</sup>] shows one of his experiments which he uses to support his view. Although castrate, these dogs' pituitary glands are intact, and as I shall endeavor to point out later, probably were producing prolactin.

In this connection it will be recalled that Kirchesky and Benjamin<sup>20</sup> observed that estrogen administration after castration in the prostatectomized rabbit almost restored the precastration size of intraocular prostatic transplants.

Lastly, with regard to estrogen effects, we have been unable to counteract

<sup>11</sup> Huggins, C.: Harvey Lectures, series 42, pp. 148-193, 1946-1947.

<sup>12</sup> Lacassagne, A.: C. R. Soc. Biol., **113**: 590, 1933.

<sup>13</sup> deJongh, S. E.: Acta Brev. Neerl., **3**: 112, 1933.

<sup>14</sup> Burrows, H. and Kennaway, N. M.: Am. J. Cancer, **20**: 48, 1934.

<sup>15</sup> David, K., Freud, J. and de Jongh, S. E.: Biochem. J., **28**: 1360, 1934.

<sup>16</sup> Korenchevsky, V. and Dennison, M.: Biochem. J., **28**: 1474, 1934.

<sup>17</sup> Burrows, H.: J. Path. Bact., **41**: 423, 1935.

<sup>18</sup> Moore, C. R. and Price, D.: Am. J. Anat., **50**: 13, 1932.

<sup>19</sup> Huggins, C. and Clark, P. J.: J. Exp. Med., **72**: 747, 1940.

<sup>20</sup> Kirchesky, B. and Benjamin, J. A.: J. Urol., **58**: 114, 1947.

prostatic weight gain in castrate rats maintained on constant doses of testosterone propionate with doses of either estradiol or stilbestrol, large, small or in between.<sup>21</sup>

Much more work is necessary.

#### EXTRAGONADAL SOURCES OF ANDROGEN AND ESTROGENS

I should now like to leave this phase of the subject and turn to a brief consideration of extragonadal sources of androgen and estrogens. This subject looms large today in connection with the rationale for bilateral adrenalectomy in the treatment of relapse after castration-estrogen therapy for disseminated prostatic cancer.

Both androgens and estrogens have been extracted from the adrenal gland, presumably the cortex. But, as in the case of the testis, this does not necessarily mean that both are made in the cortex nor in the form in which they can be isolated.

Reasons for believing that the normal adrenal cortex makes androgen and estrogen stem in part from observations on patients with either masculinizing or feminizing tumors. Yet, I beg that this is an abnormal situation and one in which there is distinct cellular alteration. In the mouse, Price<sup>22</sup> has suggested that the X-zone has an andromimetic function, and many people have accepted this. Yet, experiments by Jones<sup>23</sup> indicate that the X-zone does not secrete an androgen, since in hypophysectomized, castrated mice whose X-zones are maintained in a histologically normal state with gonadotrophin, the prostate and seminal vesicles are atrophied to the same extent as those of untreated, hypophysectomized, castrated mice.

Recently in a comparative study of the effect of castration on the spontaneous running activity of wild and domestic rats, Dr. Curt Richter<sup>24</sup> observed that whereas the adrenals of the wild rat showed considerable hyperplasia after castration and spontaneous running activity was little altered, the seminal vesicles and prostates of these animals remained atrophic. This would suggest that the hypertrophied adrenals made a cortisone-like substance but not a secondary sex gland stimulating androgen.

Time does not permit further discussion of this important phase of the problem and certainly it remains unsettled. However, no less of an authority than Dr. George Sayers of the University of Utah<sup>25</sup> concludes a recent discussion of the subject by stating that adrenal cortical androgens are not likely to have an important role in man, since a compensatory increase in androgen secretion by the adrenal cortex, if it does occur, is not of sufficient magnitude to prevent the development of deficiency symptoms following castration of the human male.

In leaving this phase, if you are not already thoroughly confused, you perhaps will be, as I was, when I saw the following sections: Slides 21 and 22 (fig. 1) are sections from the enlarged, obstructing prostate of a male, age 60, castrated at

<sup>21</sup> Grayhack, J. T., Kearns, J. W., Bunce, P. L. and Scott, W. W.: Unpublished data.

<sup>22</sup> Price, D.: *Am. J. Anat.*, **60**: 79, 1936.

<sup>23</sup> Jones, I. C.: *Endocrinol.*, **45**: 514, 1949.

<sup>24</sup> Richter, C. P. and Uhlenhuth, E. H.: Unpublished data.

<sup>25</sup> Sayers, G.: *Physiol. Rev.*, **30**: 241, 1950.



A



B

FIG. 1. Sections from prostate gland of a man, aged 60 years, whose testes were removed at age of 28 years because of tuberculous epididymitis and orchitis. A shows typical benign prostatic hyperplasia; B shows classic squamous metaplasia. Both sections  $\times 150$ .

age 28. One shows typical hyperplasia and one classic squamous metaplasia. If these are androgenic and estrogenic effects, respectively, as some believe, action must have either occurred prior to castration some 32 years before, developed after as a result of hormones formed extragonadally, or hormones had nothing to do with it.

Studies in many animals indicate that profound changes occur in the pituitary gland after castration. So-called castration cells appear in the anterior lobe, and urinary gonadotrophins, thought to arise in the pituitary, increase markedly. These changes can largely be prevented by the administration of either androgen or estrogen. On a weight basis more of the former is required.

#### THE HYPOPHYSIS AND PROSTATIC GROWTH

For years it has been known that the hypophysis, or pituitary gland, exerts a regulatory effect on the testes and on the prostate gland. Heretofore, growth stimulation of the prostate by the pituitary was considered to be entirely dependent upon intact testes, i.e., a pituitary principle known as interstitial-cell-stimulating-hormone (ICSH) stimulates the interstitial cells (Leydig cells) to produce androgen which in turn stimulates prostatic growth. In part this must be true for pituitary gonadotrophins will partially restore the prostate which has undergone atrophy following hypophysectomy. Androgen will also (slide 10 [based on data from table 3<sup>3</sup>]), but recently Dr. Grayhack and I have observed that the prostates of hypophysectomized castrate rats are less responsive to testosterone propionate than those of non-hypophysectomized castrates. Comparing groups H and D in this slide one can see that the prostate glands of those castrate rats whose pituitaries were intact (D) responded much more to an identical dose of androgen than did those castrate rats who were also hypophysectomized (H). Until recently we had no explanation for this. This explanation, if it truly is one, is the result of a combination of an accidental observation, a hunch and experimental application. It may interest you. Approximately one year ago Sonnenberg and co-workers<sup>26</sup> were studying the distribution of radioactive prolactin in the female rat. Prolactin, you will recall, is the pituitary lactogenic hormone. Strangely enough, they observed concentration of this material in the ovary *not* the breast. A few male rats were studied and again strangely enough this material was concentrated in the prostate *not* the testis. Learning of this, we had a hunch that prolactin would increase the responsiveness of hypophysectomized castrate rats to testosterone. Experimentally, Doctors Grayhack, Kearns, Bunce and your speaker<sup>21</sup> have found this to be true.

In prolactin then we have another prostate stimulating hormone, and of added interest is the previous observation of others that estrogen inhibits either the release of prolactin from the pituitary or its action after release.

In the time that remains, I should like to skim over the results of the work in our laboratory which deals with efforts to induce inhibition of prostatic growth by chemical means other than by the administration of estrogens which has been discussed in part previously. These efforts have included attempts to interfere with sex hormones from the time of injection or ingestion, during their course through the circulation, especially the liver, to the time when they reach the particular end organ such as the prostate gland. They have included a study of most hormones thought to be concerned with prostatic growth whether these

<sup>26</sup> Sonnenberg, M., Money, W. L., Keston, A. S., Fitzgerald, P. and Godwin, J. T.: J. Clin. Endocrinol., 11: 747, 1951.

hormones are derived from the pituitary, the testes, the adrenals or the thyroid. The prostate gland itself has been studied from the standpoint of whether or not it is an endocrine gland.

#### THE SITE OF INJECTION AND THE ROLE OF THE LIVER

Since Zondek<sup>27</sup> in 1934 first demonstrated that the liver inactivates estrogens, numerous investigators have studied the role of the liver in sex hormone metabolism. These studies are of practical importance when one considers that orally administered hormones are first presented to the liver, a situation which does not obtain when parenteral routes of administration are used. The following experiments performed largely by our present assistant resident, Dr. John T. Grayhack,<sup>3</sup> have a direct bearing on this problem. In this work, Dr. Grayhack used the technique devised by the Biskinds<sup>28</sup> which needs a word of explanation. By measuring the differential growth response of secondary sex glands, such as the uterus or prostate, in female or male animals in whom the gonads have been removed, to either subcutaneous or splenic implants of estrogen or androgen, one can determine the effect of the liver on hormonal action.

Under conditions of normal feeding, implanting pellets of estrogen into the spleen fails to reverse uterine atrophy induced by oöphorectomy, whereas under identical conditions, implanting estrogen pellets subcutaneously, will. The recent work of Kirgis and Rothchild<sup>29</sup> in the human is consistent with these observations in animals. They report that: "Seven ovariectomized women with mesenteric estradiol implants showed little cornification, and a high incidence of menopausal symptoms up to four months postoperatively, while four similar women, with rectus estradiol implants, showed a high level of vaginal cornification and no menopausal symptoms up to seven months postoperatively.

In the animal, under conditions of experimental cirrhosis, liver damage secondary to carbon tetrachloride feeding or during inanition, particularly protein deficiency, the liver fails to inactivate estrogen implants in the spleen.

Our work indicates that androgens are dealt with by the liver in a different fashion. For example: severe liver damage by carbon tetrachloride (slide 11 [fig. 1<sup>3</sup>]), to the point where it is estimated that at least 50 per cent of the liver parenchyma was severely damaged, failed to permit sufficient androgen to pass through the liver and cause prostatic growth in the castrate rat (slide 12 [based on data from table 1<sup>3</sup>]). In group A, with intact testes and fed a stock diet, the total prostate weight averaged 550 mg. In group B, with intact testes and fed the same stock diet *but* who were injected with carbon tetrachloride, the prostates weighed somewhat less, averaging 390 mg. Group C represents castrate rats fed stock diet. Their average prostate weights were 58 mg. Group D represents castrate rats fed stock diet and injected with carbon tetrachloride. Their average prostate weights were in the same range, 66 mg. Animals in groups E and G had pellets of testosterone implanted in their spleens. Both groups were castrate and fed stock diet. Group G differs from group E in that in G liver

<sup>27</sup> Zondek, B.: *Skandinavisches Arch fur Physiologie*, 70: 132, 1934.

<sup>28</sup> Biskind, M. S. and Biskind, G. R.: *Endocrinol.*, 32: 97, 1943.

<sup>29</sup> Kirgis, H. and Rothchild, I.: *Endocrinol.*, 50: 269, 1952.

damage was caused by carbon tetrachloride. In spite of this, sufficient androgen did not get through the liver to cause prostatic growth. That the prostate was responsive to androgen is illustrated by groups F and H. Here testosterone was implanted subcutaneously, and in spite of severe liver damage secondary to carbon tetrachloride injections, the prostate of the castrate rat grew rapidly in response to androgen, H. (Compare G and H in concluding this phase.)

The results of a similar study involving complete starvation are substantially the same and again show that the liver continues to inactivate androgen under conditions of stress. We can conclude this phase with the statement that it seems that even under severe stress the liver is a "physiological filter" for testosterone propionate and probably for other androgens but not for estrogens. A hint that this may hold for man is suggested by the observations in World War II that male prisoners, when starved and for a short time after feeding, developed gynecomastia.

As yet no clinical use has been found which embraces these observations, and yet in time one may be. Last year, two members of our resident staff, Doctors Grayhack and Harris,<sup>30</sup> explored the possibilities of creating an adrenal shunt in the dog in an effort to cause the liver to inactivate adrenal androgens. In so doing their thought was that such a procedure in man might be of importance in the treatment of the invariable relapse following castration-estrogen therapy for disseminated prostatic cancer. Using the technique illustrated in slide 13 [fig. 1<sup>30</sup>] they succeeded in causing left adrenal blood to first traverse the liver (fig. 2). If an excretory urogram revealed left kidney function, the right adrenal gland could be removed and the animal would live. At present the feasibility of such a procedure in humans with advanced prostatic cancer is being investigated.

Time does not permit a detailed consideration of the effect of dietary alterations on the prostate-stimulating action of parenterally administered androgen. However, at this time work in our laboratory suggests that a specific dietary substance, probably a protein, is necessary for maximal action of testosterone. We are presently engaged in studies designed to tell us the nature of this protein in an effort to eliminate it from the diet, or if possible, to find chemical means of interfering with its action.

Before concluding this phase of the subject, I wish to state a specific example of how the absence of a specific dietary substance can interfere with the action of a sex hormone, and how certain chemical substances can bring about this action independent of dietary restriction of this specific dietary substance.

For the last 5 years it has been known that the vitamin, folic acid, is necessary for the action of estrogenic hormones.<sup>31</sup> This has been determined by experiments in which folic acid has been eliminated from the diet. Three years ago, Dr. Herbert Brendler,<sup>32</sup> working in our laboratory, found that a chemical substance, bearing the trade name Aminopterin, and also known as an anti-folic acid compound, or an antivitamin, could effectively inhibit the action of estrogen on the

<sup>30</sup> Grayhack, J. T. and Harris, A. P.: Method for establishing portal drainage of adrenal venous blood in dogs, with metabolic studies included. In press, *J. Urol.*

<sup>31</sup> Hertz, R.: *Endocrinology*, **37**: 1, 1945.

<sup>32</sup> Brendler, H.: *Science*, **110**: 119, 1949.

rat prostate even though the diet was adequate in folic acid. Slide 14 [table 1<sup>3</sup>] illustrates his experiments in part. Referring only to experiment one, we observe that alpha-estradiol will shrink the prostate gland of the intact adult rat when given alone, but the same dose in combination with Aminopterin will not. Further experiments of his proved that this action was not due to any androgenic action of Aminopterin but to its interference with folic acid. Unfortunately,

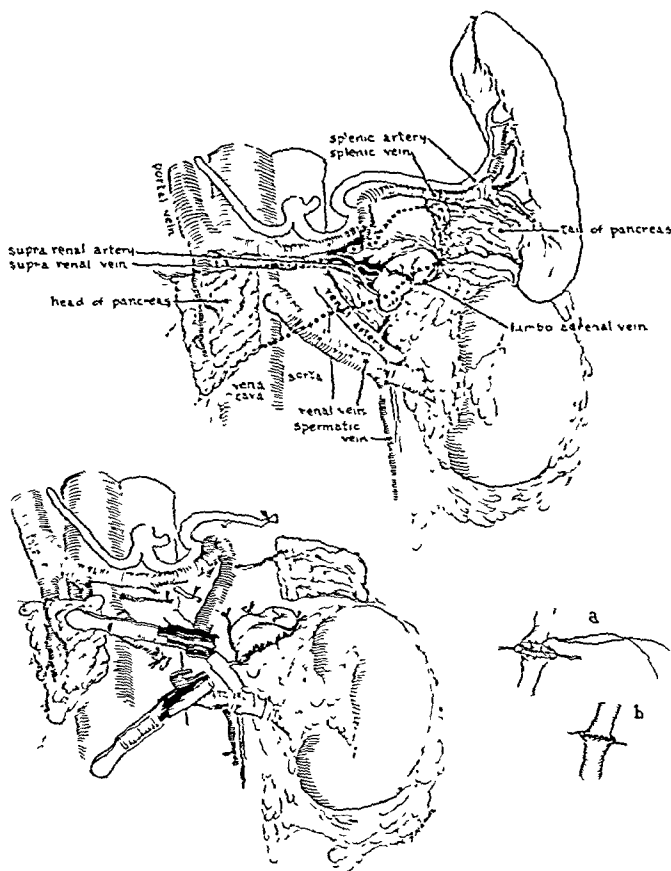


FIG. 2. Illustrating technique of Grayhack and Harris<sup>30</sup> for establishing portal drainage of venous blood from left adrenal gland of dog. Right adrenal is removed at second operation.

to date no specific vitamin has been found necessary for androgen action, thus preventing the development of an antivitamin to it. The search continues.

I shall conclude my remarks on chemical inhibitors with a few words on the search for inhibitors of pituitary action. As indicated earlier, the action of the pituitary gland on prostate growth is mediated through the testes. In recent years numerous substances have been suggested as pituitary inhibitors, notably parahydroxypropiofenone, suggested by the French,<sup>33</sup> and an extract of the

<sup>33</sup> Perrault, M.: Presse méd., 58: 1010, 1950.



weed, *Lithospermum ruderales*, suggested by Dr. Marian Drasher<sup>34</sup> of Indiana University. Both have been without effect when tested on rats in our laboratory, neither causing any decrease in testicular or prostatic size or observable function. Work on the latter compound continues, primarily because of the rather authentic reports that the Western American Indians formerly brewed a tea of the weed which when taken by mouth was said to have contraceptive properties. Dosage was expressed in P-P units (papoose-preventing).

In what little time remains, I should like to relate briefly how knowledge gained in the laboratory has helped us in the clinical care of the patient with disseminated prostatic cancer.

It is now over 12 years since Dr. Charles Huggins and Dr. C. V. Hodges,<sup>35</sup> the latter now of your Section, demonstrated the profound beneficial effects of castration and/or estrogen therapy in the treatment of this disease. Doctor Huggins will tell you that this work was largely the result of study of hormonal action in the fistula dog.

Encouraged with the results, but dissatisfied with eventual relapse, Huggins and his associates continued to investigate the problem. Again, on the basis of animal studies suggesting that the adrenal produced androgen and thus leading us to believe that adrenal androgen was responsible for relapse, together we attempted to maintain life after bilateral adrenalectomy in the prostatic cancer victim relapsing after castration and estrogen therapy. We were only partially successful.<sup>36</sup> Now with cortisone we can with ease, and it has been the experience of our now separate groups that over half receive distinct benefit from this procedure.

Recently, we in our laboratory have pushed the mechanism back one step further, observing profound atrophy of a prostatic cancer, as well as considerable general improvement, in a single patient in whom hypophysectomy was done.<sup>37</sup> The fact that this patient's testes and adrenals were surgically intact prior to hypophysectomy indicated to us, in the light of observations in animals, that this action was mediated at least through the testes and possibly the adrenal.

In concluding I hasten to admit that this has been a long and rambling discourse, devoid of synthesis, and yet the facts prevent the telling of a simple story of what makes the prostate grow. Apropos are the words of Hermann von Helmholtz, renowned physicist, physiologist and physician, in his masterful lecture "Dan Denken in der Medizin,"<sup>38</sup>:

"To one who has to contend with the hostile forces of fact, indifference and romance disappear; that which he knows and can do, is exposed to severe tests; he can only use the hard and clear light of facts, and must give up the notion of lulling himself in agreeable illusions."

<sup>34</sup> Drasher, M. L. and Zohl, P. A.: *Exper. Biol. & Med.*, **63**: 66, 1946.

<sup>35</sup> Huggins, C. and Hodges, C. V.: *Cancer Res.*, **1**: 293, 1941.

<sup>36</sup> Huggins, C. and Scott, W. W.: *Ann. Surg.*, **122**: 1031, 1945.

<sup>37</sup> Grayhack, J. T., deKlerk, J. N. and Scott, W. W.: Unpublished data.

<sup>38</sup> von Helmholtz, H.: *Bull. Inst. Hist. of Med.*, **6**: 117, 1938.

## RESULTS OF PALLIATIVE TREATMENT OF EARLY CARCINOMA OF THE PROSTATE

ROGER W. BARNES

*From the Department of Surgery (Urology), School of Medicine, College  
of Medical Evangelists, Los Angeles, Calif.*

A great difference of opinion exists among urologists as to whether radical removal of the prostate, including its capsule and the seminal vesicles, is indicated when a diagnosis of early carcinoma is made. Some contend that radical surgery cures a sufficient number of these cases to warrant doing the operation, while others claim that the average length of life is as great, and that the patient lives with more comfort and satisfaction, when he is treated without radical surgery. A number of series of cases have been reported that give the results of radical total perineal prostatectomy for early carcinoma of the prostate, but we have been unable to find a comparative series which gives the results of palliative treatment of similar cases. This paper is presented in an effort to provide such a comparison.

It would obviously be impossible to select cases of early carcinoma of the prostate having had palliative treatment which would be an exact duplicate of a reported series with radical surgery. However, by adhering to the criteria which are used for selection of cases for radical total perineal prostatectomy, it is possible to select a series of cases having palliative treatment which would be similar enough to the reported radically operated cases to make a comparison valuable; and by following the former for a sufficient length of time the original diagnosis of early carcinoma can be confirmed in most cases.

The criteria used in the selection of cases for this study are as follows:

- 1) Localized hard area palpable in the prostate through the anterior rectal wall.
- 2) Prostate not fixed.
- 3) No palpable evidence of extension of induration beyond the prostatic capsule.
- 4) All cases were followed five years or longer.
- 5) The original diagnosis of carcinoma was confirmed either by microscopic examination of tissue following subsequent transurethral prostatic resection, or by developing typical clinical findings of carcinoma. It is probable that a few cases of carcinoma which regressed and remained stationary were eliminated by this criterion.

A total of 738 cases of carcinoma of the prostate were processed. Fifty-one, or 6.9 per cent, of these were diagnosed as early. This compares favorably with the 5 per cent to 6 per cent which most authors state is the approximate proportion of prostatic carcinoma which is suitable for radical perineal prostatectomy. Twenty of these cases were eliminated because they did not meet all of the foregoing criteria; some because the diagnosis was not subsequently confirmed, and others because recent follow-up reports were not available. This leaves 31 cases,

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 20, 1952.

upon which this study is based; it is 4.2 per cent of the total number of 738 cases which were processed. Sixteen, or 53 per cent, of the 31 patients studied lived 5 years or longer, and 7, or 22 per cent, lived 10 years or longer. Of the 15 patients which died in less than 5 years, the cause of death in 5, or 33 per cent, was cardiovascular or other lesions not due to prostatic malignancy.

A comparison of these data with reports of longevity following radical perineal prostatectomy is given in table 1. A comparison of the 53 per cent 5-year survival in the cases having palliative treatment and the 51 per cent to 56.5 per cent in those having total prostatectomy, shows no significant difference between the two groups. In the reports of cases in which the patients underwent radical surgery, most of those surviving are reported as having no evidence of recurrence or of metastases; whereas in the cases having palliative treatment reported here there were 6, or 38 per cent, of the 16 cases surviving more than 5 years which had definite clinical evidence of prostatic carcinoma at or sometime after the end of the 5-year period. Therefore even though the difference in the survival period is the same in the two groups, the difference in the apparent "cure" rate is significantly better in those patients who have radical surgery.

TABLE 1. *Early carcinoma of the prostate. Comparison of survival following palliative treatment with that following radical total perineal prostatectomy*

|                                         | NO. CASES<br>REPORTED | 5-YEAR<br>SURVIVAL | 10 YEAR<br>SURVIVAL |
|-----------------------------------------|-----------------------|--------------------|---------------------|
| Palliative (Barnes)                     | 31                    | 53%                | 22%                 |
| Radical (Jewett) <sup>1</sup>           | 78                    | 51%                | 28%                 |
| Radical (Twinem & Davalos) <sup>2</sup> | 48                    | 55%                |                     |
| Radical (Hinman) <sup>3</sup>           | 23                    | 56.5%              |                     |
| Radical (Colby) <sup>4</sup>            | 34                    | 55%                |                     |

The palliative treatment given to this series of cases was as follows: All but 6 of the 31 cases had endocrine therapy—most of them stilbestrol; bilateral orchiectomy was done on 10. Seven had deep x-ray therapy and in 28 cases a transurethral prostatic resection was done for relief of obstructive symptoms sometime during the time that the patients were kept under observation.

#### SUMMARY

The results of palliative treatment of early carcinoma of the prostate are compared with those of radical perineal prostatectomy as reported by other authors. The 5-year survival period was almost identically the same in the two groups of cases, and the 10-year survival period was 6 per cent better in one reported group which had radical surgery than in those having palliative treatment. Cases reported as having no evidence of the disease at the end of the 5- and 10-year periods are significantly greater following radical surgery than in those having palliative treatment.

1216 Wilshire Blvd., Los Angeles 17, Calif.

<sup>1</sup> Jewett, H. J.: *J. Urol.*, **61**: 277, 1949.

<sup>2</sup> Twinem, F. P. and Davalos, A.; *J. Urol.*, **61**: 575, 1949.

<sup>3</sup> Hinman, F. Jr.: *Calif. Med.*, **68**: 338, 1948.

<sup>4</sup> Colby, F.: *Surg. Cl. of N. Amer.*, **27**: 1307-1311, 1947.

## TREATMENT OF CARCINOMA OF THE PROSTATE

R. H. FLOCKS

*From the Department of Urology, State University of Iowa Hospitals, Iowa City, Iowa*

It is the purpose of this report to outline therapy for carcinoma of the prostate upon the basis of a series of 854 patients with carcinoma of the prostate seen at the University Hospitals from January 1, 1926, to July 1, 1945; a study of individual patients that have been followed for less than 5 years; and the results of other observers which have been reported in the literature.

This experience has amply demonstrated that these patients must be treated upon an individual basis. In some, the presence of coincidental disease processes makes a try at curative therapy out of the question (fig. 1). Age, temperament, home environment, sexual status and many similar factors must be considered before an outline of treatment is planned.

With regard to the fact of the cancer itself, these patients may be divided into three groups: 1) the cancer is limited to the prostate itself; 2) the cancer extends beyond the prostatic capsule into the periprostatic and perivesicular tissues; and 3) definite distant metastases are present.

It is generally conceded that from 5 to 10 per cent of the patients with carcinoma of the prostate, as they present themselves to the urologist for care, fall into the first group. In these cases, the carcinoma is limited to the prostate itself, and usually there is no evidence of bladder neck obstruction. The blood acid phosphatase is normal, and x-rays of the pelvis and spine reveal no evidence of metastasis. At present it is generally considered that if the general condition of the patient is good, radical prostatectomy offers the best chance for a long comfortable life for patients in this group. Recent improvements in the techniques of anesthesia, blood transfusion, the treatment of infections and in the technique of radical prostatectomy emphasize that if the lesion is limited to the prostate itself, there is at least a 50 per cent chance for a 5 year "cure." Recent developments in the technique of retropubic prostatectomy have given the surgeon two different techniques for the radical removal of the carcinoma, once the diagnosis is made. In our hands at the University Hospitals, unless the carcinoma is very close to the apex of the gland, retropubic radical prostatectomy is preferred to the perineal approach because of the ease with which the seminal vesicles, bladder neck, and regional iliac lymph nodes are exposed. The choice of operation, however, depends upon the experience of the surgeon. Both procedures have been well described in the literature.

The second group of patients with carcinoma of the prostate comprises 55 per cent of the total. These patients usually have evidences of bladder neck obstruction. The lesion has spread through the capsule, invading the periprostatic, perivesical and perivesicular tissues. Occasionally the regional lymph nodes are involved. However, no evidences of distant metastasis are present. These lesions

Read at annual meeting, Southeastern Section, American Urological Association, Boca Raton, Fla. April 5, 1952; also at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 21, 1952.

upon which this study is based; it is 4.2 per cent of the total number of 738 cases which were processed. Sixteen, or 53 per cent, of the 31 patients studied lived 5 years or longer, and 7, or 22 per cent, lived 10 years or longer. Of the 15 patients which died in less than 5 years, the cause of death in 5, or 33 per cent, was cardiovascular or other lesions not due to prostatic malignancy.

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cannot be satisfactorily removed by radical prostatectomy. They could conceivably be removed by viscerectomy; but since this procedure rarely accomplishes complete removal of involved lymphatics, and these patients average over 70 years of age, it is rarely indicated. In the majority of cases in group 2, the therapy has consisted in the past of transurethral prostatic resection to relieve the patient of obstruction and hormonal therapy for palliation.

Is it possible to achieve in this group what may be accomplished in group 1 by radical prostatectomy? Viscerectomy is being tried, but is applicable in the author's opinion for a very few of these patients. The hormonal attack, thus far, has produced only palliation. Radiation with radium and roentgen rays has been used as a third method of therapy. The report of Deming, which analyzed 100 cases treated by radiation with x-ray and radium, shows definitely that, given

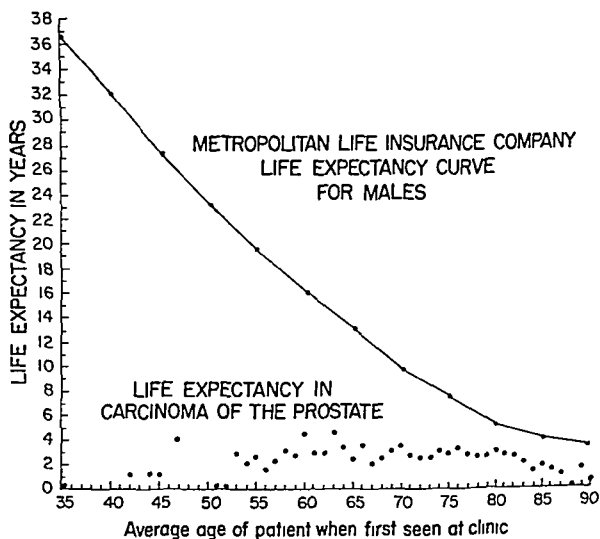


FIG. 1. Life expectancy curves. Note that with conservative management, as carried out up to 1945, there is a marked difference between patients with carcinoma of prostate and general population. This is particularly true of those under age of seventy.

intensive radiation, most of these tumors respond to some extent. However, with such intensive radiation, complications resulting from the effect upon surrounding tissues made this type of treatment prohibitive. Severe bowel and bladder irritation and ulcerations developed; and, because of these complications, the necessary massive dosage to the tumor could not be delivered.

For the past year, the author, in conjunction with members of the Department of Radiology, has utilized radioactive isotopes in the treatment of this type of carcinoma of the prostate. It is possible, by the use of a selected isotope, such as Au198, to give more localized and intensive radiation because of the characteristics of the isotope and the neoplasm. Radioactive gold, Au198, in colloidal solution is non-toxic in therapeutic doses and will remain, for the most part (90 per cent), at the site of injection when instilled into tissue. Its half-life is 2.7 days and about 90 per cent of the energy released is in the form of beta radiation, with a maximum range of 3 mm. in tissue. This means that intensive radiation occurs

only in the immediate area around foci of the isotope and does not extend more than a few millimeters beyond this point. Thus, it seems possible, by direct infiltration of radioactive gold solution to give a cancericidal dose of radiation and still circumvent most of the objectionable side complications in the rectum and bladder associated with radium, radon, and roentgen therapy. About 97 per cent of the radiation is delivered over a period of one and a half weeks, and, instead of radiating from 10 to 15 sources, the colloidal gold sets up literally billions of point sources of highly ionizing beta radiation. There is also evidence that indicates that enough radioactive material is taken up by the lymphatics and delivered to the regional lymph nodes so that metastatic neoplasm in these nodes is affected.

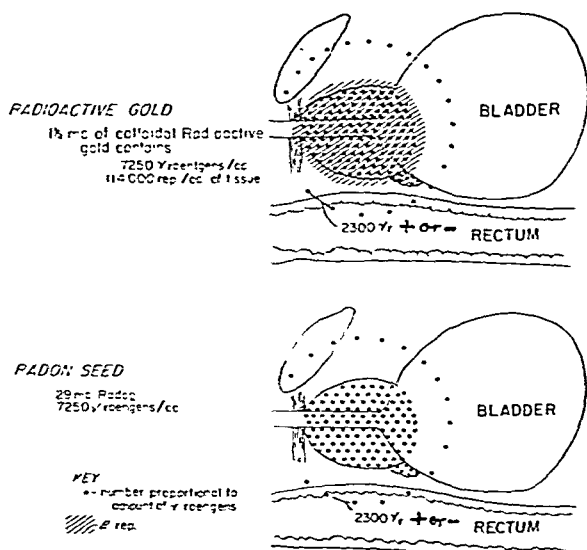


FIG. 2. Diagram showing what could theoretically be accomplished with radioactive gold Au 198 as contrasted with radon seeds in prostate involved with carcinoma to volume of 35 cc. In one case one and a half mc of colloidal radioactive gold are infiltrated ideally throughout the tumor giving approximately 7250 gamma roentgens and 114,000 roentgen equivalent physicals per cc of tumor. Note that carcinoma gets the gamma dose plus the tremendous beta dose. Only the gamma produce the approximately 2300 gamma roentgens 1 cm. from the margin of growth.

In contrast, same tumor with 29 mc of radon evenly distributed gives about same gamma dose to tumor and surrounding structures, but does not have intensive beta radiation within tumor area.

By using the suprapubic approach, it is possible to expose the prostate, the lymphatics about the rectum, the regional lymph nodes, and the seminal vesicles and adjacent lymphatics so that visualized or palpable tumor can be thoroughly infiltrated with the radioactive material. Since the total volume of the carcinoma is relatively small, (rarely over 150 cc), it is possible to give massive doses of radiation to the tumor tissue, and at the same time keep the total dose small. The layers of fascia about the prostate and seminal vesicles with their vessels and lymphatics form a fascial compartment about these structures and this aids in holding the radioactive solution in the desired location. All of these factors make the treatment of carcinoma of the prostate by interstitial radiation with a radioactive isotope, such as Au198, seem very promising (fig. 2).



Thus far, 69 patients have been treated with Au198. The technique consists essentially of exposing the carcinoma and regional lymph nodes and seminal vesicles through a suprapubic approach and thoroughly infiltrating the entire area with a solution of the radioactive isotope. The usual dose is from 50 to 150 millicurie of the radioactive gold in colloidal solution diluted to total volume of about 20 cc. An attempt is made to vary the total amount depending upon the volume of the carcinoma to be infiltrated. In small glands, approximately 1 to 1.5 millicurie per cubic centimeter of tissue to be infiltrated is used. In the larger glands, much less is used, since the total amount to be infiltrated should not exceed 150 millicurie, because with such a large dose the effect of the gamma radiation becomes significant.

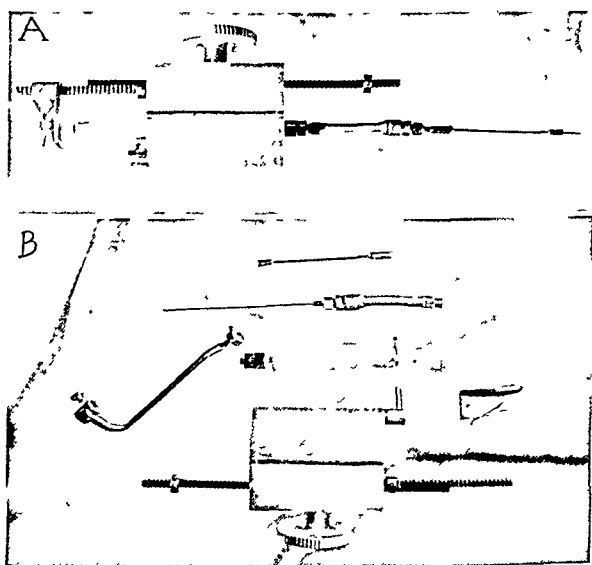


FIG. 3. Protected syringe with pressure arrangement for injecting radioactive gold into prostatic tumor.

The problem of distribution is still not completely solved. The best way to get good distribution of the material throughout the carcinoma and to protect the operator from the effects of the radiation, and, at the same time, not penetrate the capsule towards the region of the rectum is to use a syringe as illustrated (fig. 3). This syringe is covered with sufficient thickness of lead to protect the operator and has a screw-type pressure arrangement which causes the material to enter with great force throughout the tissue without the necessity of penetrating the tissue deeply with the needle and, thus, risking deposition of the material beyond the protective fascias. Care must be taken at all times that the needle does not penetrate the capsule toward the rectum so that no puddles of radioactive material are deposited in the rectal wall. Some of our difficulties in the early cases were upon this basis. Radiation hazards must be, and are, readily controlled under the direction and with the advice of a radiologist thoroughly trained in the use of radioactive isotopes (fig. 4).

The early results of the treatment in the first 20 cases have been described by Flocks, Kerr, Elkins, and Culp and reported to the North Central Section of the American Urological Association on October 5, 1951. Since that time, 49 more cases have been thus treated, and, in general, the findings have been of great promise and have confirmed the earlier results. There have been no cases of bladder irritation following this type of interstitial radiation. There have been rectal difficulties of a varying degree of intensity in approximately one-third of the



FIG. 4. *A*, illustrates filling of syringe with radioactive gold in preparation for injection. Guarded syringe is then handed to surgeon for the injection, as illustrated in figure 2. *B*, illustrates prostate exposed and material being injected. Note lead guarded syringe.

cases. In some of these, ulceration has occurred; but, in all, adequate control has been possible by medical means with the exception of 1 case in which a colostomy was necessary. There was 1 case of idiosyncrasy to the gold itself which caused death. In all cases, rapid and very marked decrease in the size of the tumor occurred and over 50 per cent of these cases, thus far, are clinically apparently completely controlled (fig. 5). The first case receiving this treatment was in March 1951. This patient was last examined on February 26, 1952. He is voiding well. Rectal examination reveals no evidence of tumor. His last negative biopsy was in June 1951, and there has been no change in his findings since then. In those

cases in which similar results were not obtained, there has been evidence of residual tumor. Usually this occurred in patients who had very large neoplasms to begin with and in which, therefore, adequate distribution and adequate interstitial radiation was not obtained. The smaller lesions have responded very well because they were much more easily infiltrated with adequate dosage. Of course, it is still too early to know what the ultimate results will be. There is, however, no question that even by the method used at the present time tremendous destruction of the tumor and, in some cases, apparently complete eradication has occurred. It may very well be that better results will be obtained when interstitial

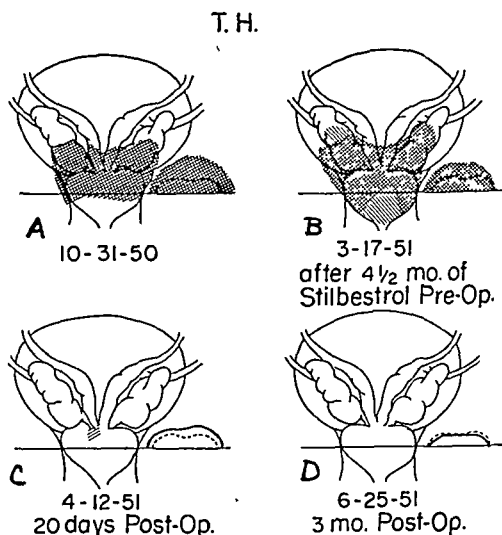


FIG. 5. Case 1. T. H., aged 80, admitted to University Hospitals on March 16, 1951, with known carcinoma of prostate of 5 months' duration; patient had been on hormone therapy for 4½ months. Pathologic diagnosis: carcinoma of prostate.

A shows rectal findings on October 31, 1950. B shows rectal findings on March 17, 1951. On March 23, 1951, 70 mc. of Au 198 was infiltrated into tumor. Its volume was estimated at 35 cc. At time of operation, both seminal vesicles and both lateral lobes and periprostatic tissue on each side were involved. The lymph nodes could not be palpated. C shows rectal findings on April 12, 1951, 20 days postoperative. Transurethral biopsy on April 16, 1951, still showed carcinoma, but also showed extensive degenerative changes. Tissue biopsy removed transurethrally on June 26, 1951, showed no evidence of cancer. The rectal findings on June 25, 1951, were essentially negative and are illustrated in D. This case was last examined on February 26, 1952. He was normal at that time.

radiation is combined with hormonal treatment and some type of surgical treatment. In two cases, residual masses of carcinoma were eliminated by a second injection through perineal needles.

Thus, the treatment of those cases of carcinoma of the prostate which fall into the second group presents a fascinating problem. Newer developments in interstitial radiation, utilizing beta radiation, may radically alter the entire treatment of this group of patients, and also those of group 1. The early results of treatment of this group with Au198 are promising. However, radiation hazards must always be kept in mind and taken into account.

The treatment of those patients who fall into group 3 is essentially palliative. It consists of relief of bladder neck obstruction by transurethral resection, con-

servative prostatectomy or suprapubic cystostomy followed by and in conjunction with hormonal therapy. The results of 854 patients treated by conservative methods at the University Hospitals ending with the period 1945, is illustrated in table 1. From these experiences, it is apparent that endocrine control of the neoplasm is, practically speaking, purely palliative as carried out at the present time. There is no question, however, that the endocrine therapy of carcinoma of the prostate which has been used extensively since the 1941 reports of Huggins and Munger has revolutionized the status of the patients with inoperable carcinoma of the prostate. In the vast majority of these patients, such therapy yields dramatic improvement: relief of pain, decrease in size of the original tumor and its metastasis, and general improvement. This gratifying result, however, with the exception of the relief of pain which may be lasting, is only temporary and its duration varies from a few months to several years. The mechanisms of this control and the reasons for its failure with the lapse of time are not completely

TABLE 1. *Treatment of series of 854 patients with carcinoma of prostate ending July 1, 1945. Results are given following five or more years of follow up*

| TREATMENT                     | TOTAL CASES | OF 5 YR. SURV. | % OF 5 YR. SURV. | % WITH LATER TREATMENT | AVG. SURV. | AVG. AGE |
|-------------------------------|-------------|----------------|------------------|------------------------|------------|----------|
| TUR only                      | 335         | 41             | 12.2             | 20.6                   | 2.22       | 72.1     |
| TUR with stilbestrol later.   | 79          | 34             | 43               | 44.4                   | 4.52       | 70.5     |
| TUR and immediate x-ray       | 42          | 1              | 2.4              | 14.3                   | 1.26       | 67.8     |
| TUR, x-ray, stilbestrol later | 2           | 0              | 0                | 0                      | 2.48       | 61.5     |
| Palliative x-ray              | 20          | 3              | 15.0             | 15                     | 2.17       | 65.5     |
| Stilbestrol first             | 64          | 13             | 20.0             | (TUR) 34.4             | 2.69       | 69.9     |
| TUR, stilbestrol initially..  | 256         | 59             | 23.0             | 11.3                   | 2.63       | 72.5     |
| No treatment at S.U.I..       | 53          | 0              | 0                | 1 (S-P)                | —          | —        |
| X-ray and later stilbestrol   | 3           | 0              | 0                | 0                      | 2.50       | —        |
| Total cases                   | 854         | 151            | 17.68            | 19.67                  | 2.54       |          |

understood at the present time. From the results reported by Nesbit and from our own experiences, it would seem that the combined influence of orchiectomy and stilbestrol is superior to that of stilbestrol alone. There is no evidence that large doses as compared with smaller doses of stilbestrol or other estrogens make a difference in the control of the neoplasm. If anything, smaller doses seem preferable. The recent report of Parke Smith on the use of Tace, a synthetic estrogen which does not stimulate the pituitary to the same extent and in the same way that other estrogens do, is of interest. But this drug has not been used long enough to know about its ultimate effects. Huggins has recently performed bilateral adrenalectomy in selected cases upon the premise that secretions from the cortical portion of the adrenals counteract the influence of orchiectomy. It is too early to evaluate his results. Scott recently reported improvement in a patient with extensive metastasis following pituitary extirpation.

The inter-relationships between endocrine balance and carcinoma of the pros-

tate present many interesting facets. At the present time, however, from a practical point of view only this can be said: The best type of palliation in those patients who have carcinoma of the prostate not amenable to destruction either by radical surgery or interstitial radiation can be accomplished by orchiectomy combined with estrogen therapy added to whatever surgical procedure is necessary to relieve bladder neck obstruction.

#### SUMMARY

In summary, then, the treatment of carcinoma of the prostate depends upon the extent of the neoplasm and the general condition of the patient. In those lesions limited completely to the prostate, if the general condition of the patient warrants it, radical removal of the prostate by either the perineal or retropubic route may be carried out. The retropubic technique offers more extensive exposure of the regional lymph nodes and the seminal vesicles and possibly, therefore, permits a little more radical removal of the carcinomatous area. A great deal of this, however, depends upon the experience of the surgeon. In those cases where the carcinoma has extended beyond the capsule of the prostate and is, therefore, inoperable by radical prostatectomy, interstitial radiation using radioactive isotopes emitting, primarily, beta radiation seems promising. The results of early experiences in 69 patients with interstitial radiation with Au198 are briefly described and discussed. In those patients with carcinoma of the prostate where the lesion has metastasized so that the previously described methods of treatment cannot be used, the treatment is completely palliative and consists essentially of relief of bladder neck obstruction by transurethral resection, conservative prostatectomy or suprapubic cystostomy and endocrine control of the neoplasm by orchiectomy and estrogen administration. When the neoplasm of such patients becomes refractory to orchiectomy and estrogens and the general situation warrants it, bilateral adrenalectomy may be considered.

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## THE USE OF ESTROGEN THERAPY PRELIMINARY TO RADICAL PERINEAL PROSTATOSEMINAL VESICULECTOMY IN CARCINOMA OF THE PROSTATE

JOHN J. SULLIVAN AND CARL H. HARTWIG

During the past 6 years, we have performed radical perineal prostatoseminal vesiculectomy for carcinoma of the prostate in 12 cases. All except the first case had received varying amounts of female sex hormone prior to surgery. This report presents a review of our experience with this combined plan of treatment. The number of cases is insufficient to warrant any excursion into statistics. Besides, our ideas on dosage have changed during this period, which means that all cases were not treated alike. Furthermore, insufficient time has elapsed to permit any final conclusions. Despite these limitations, we believe that these few cases deserve to be reported, first because ten of the twelve represent patients who were originally inoperable for technical reasons who became operable under the administration of estrogen. Secondly, we find that the response of the carcinomatous nodules under estrogen therapy is a valuable aid in diagnosis.

Our mortality rate has been low, our morbidity acceptable, and all patients but the one who died are back at their former occupations. Compared with previous methods of treatment, these people represent salvaged material.

Colston suggested the possibility of employing this regimen in 1944, and John K. Ormond in his paper on "Radical Perineal Prostatectomy for Carcinoma," read before the section on Urology of the AMA in San Francisco in July 1946, mentions one such case. Since then, several groups of authors have reported their experiences.

Colston and Brendler, in 1947, reported 7 cases out of 200 patients with carcinoma of the prostate seen in 3 years at the Brady Institute. One of these died of metastases 1 year after operation. They stated that estrogen causes regression of the prostate in 75 per cent of cases, and regression of the metastases in 45 per cent. Since the younger peripheral cells are more androgen dependent, these are the first to regress; the original central tumor cells are left, to be sure, but the cells lying in the area of surgical excision are destroyed or changed. Colston gives Vallett the credit for performing a radical perineal prostatectomy after orchiectomy in 1944.

W. W. Scott and Parlow, in 1949, report having operated upon 14 cases, of which 9 were used as the basis for their paper, the rest being omitted because insufficient time had elapsed since operation. In 1951 these same authors reported an enlarged series of cases. In this paper, two cases are reported in which radical prostatectomy had been done, and no carcinoma found, the carcinoma apparently having been replaced by nests of connective tissue. They recommend giving postoperative stilbestrol, "for a very long time." We have not used hormone postoperatively. While some benefits may be derived from this procedure, on

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 21, 1952.

the other hand, it might be more wise to discontinue the estrogens after surgery, with the intention of using them later, in the event of recurrence or metastases.

In 1949, Gutierrez enthusiastically hailed this regimen as a "New Horizon in the Surgical Management of Carcinoma of the Prostate." He says that radical perineal prostatectomy had previously been possible in only 10 per cent of cases, and that the operability is now nearer 80 per cent. While this sounds a bit optimistic, I must concede that we have seen only 1 case since 1946 in which the radical procedure could have been done without previous preparation. Gutierrez is willing to go so far as to do a cystectomy plus the prostatoseminal vesiculectomy, where the carcinoma has invaded the bladder neck and trigone.

Harrison and Poutasse, in 1951, reported 19 operable cases out of 100 consecutive patients at the Peter Bent Brigham Hospital. Of these, five had estrogens for 30 to 60 days preoperatively in order to facilitate surgery. It is not definitely stated in this paper just how many the authors considered inoperable originally, and which became operable under estrogens.

Kimbrough and Rowe in 1951 reported 78 cases in which 39 had radical operations. Of these, 8 had had castration and estrogens. Two more had conservative operation only, on account of their age. They express the belief that 70 per cent are amenable to radical perineal prostatectomy. We consider this unusually optimistic.

It is beyond the scope of this report to discuss surgical technique in detail. We have done the radical perineal prostatoseminal vesiculectomy in these cases because it seems to us to offer the best chance for a wide excision of involved tissue. It is not much more difficult than the conservative simple perineal prostatectomy for benign enlargement. That portion of the gland which is most often the seat of carcinoma is the first part to be exposed. It can therefore be subjected to close scrutiny and direct palpation, as well as to biopsy and frozen section in doubtful instances, before committing the surgeon to the radical operation. In one case, we proceeded with the radical operation in spite of the pathologist's report of "no carcinoma" on two pieces of tissue. Our decision was based upon the suggestive palpatory findings, as well as the rapid softening of this mass under estrogen therapy. Carcinoma was subsequently found on permanent sections. This raises the question as to whether one should not proceed with the radical operation more frequently if clinical findings are highly suggestive of carcinoma, and take the risk of occasionally removing a non-cancerous gland.

Our criteria for the diagnosis of carcinoma are not new. We rely primarily on rectal palpation, with confirmation by instrumental examination. Secondly, we are influenced by the response of indurated areas to large doses of estrogens. Characteristically, the prostate becomes movable and the lesion shrinks. The time required for this response varies widely. Where available, we use supporting evidence, such as the Papanicolaou method. Several of our early cases had frozen sections at surgery. We now schedule the radical operation without frozen section if conditions warrant. However, frozen section should be done on operable cases which have not responded to estrogens.

We do not operate on patients with demonstrable metastases, though Gutierrez recommends doing so in selected cases. We consider the patient's general

condition as a matter of course, but this age group has no gilt-edged risks. However, this procedure is remarkably well tolerated when compared with other methods, all other factors being equal. While age is no bar in itself to doing this operation, the patient should have a reasonable life expectancy. It goes without saying that the usual preoperative studies of renal function and the like are done before deciding upon surgery.

One hears of postoperative incontinence as an objection to the radical perineal operation. We no longer worry about the possibility of incontinence. All these patients have good sphincter muscles. Most of the writers mentioned earlier, specifically report good sphincter control in the majority of their patients. The re-acquisition of complete control is often dependent upon the patient's perseverance in re-educating himself. After the radical operation, the catheter urine clears more quickly, the perineal wound leaks less, and heals as quickly as if a simple perineal enucleation had been done. Modern anesthetics and antiseptics have reduced the risk to the patient, beyond our most optimistic hopes of a dozen years ago.

Until some form of non-surgical therapy is developed which will eradicate malignancies, surgical extirpation of the growth, though imperfect, is still our best hope. The acceptance of this therapeutic philosophy puts the radical perineal prostatectomy in its reasonable perspective. It is a big operation, but carcinoma is a big disease. It is a much less formidable procedure than is carried out in many other areas of the anatomy. Those patients who have accepted and undergone the procedure, all express a sense of relief at "having the thing out," a relief they could never get from management which is merely palliative. They tackle their postoperative lives with an optimistic enthusiasm, which enables them to return to a full day's work at their original occupations.

An observation worth recording at this point concerns the alteration in the periprostatic tissues after hormonal therapy. Ordinarily, the separation of the leaves of Denonvilliers' fascia is very easy in benign cases, and not difficult in operable malignant cases, except where the capsule has been invaded. After hormonal therapy, scarring occurs, making sharp dissection almost always necessary. The amounts of hormone which we have used in this series of cases has varied widely, from 120 mg. to 32,625 mg. The fear expressed several years ago that large doses cannot be tolerated is not borne out by our observations, since we frequently use from 75 to 150 mg. per day.\*

#### AGE

The patient's ages ranged from fifty to eighty, with six in the fifties, five in the sixties, and one of eighty.

#### SUMMARY

This paper reviews 12 cases of carcinoma of the prostate, eleven of which had preliminary treatment with estrogens for varying periods. The glands were originally inoperable in ten, and in one the diagnosis was in doubt, but was

\* Since this paper was read, we have done 5 additional cases. We have used up to 300 mg. of diethylstilbestrol daily without ill effects.



strengthened by the characteristic response to estrogen. The glands became movable, after which radical perineal prostatoseminal vesiculectomy was done. Our experience with this method of treatment was reported. Criteria for diagnosis and recommending operation were outlined. Reasons for adopting this operative procedure are discussed. No claim is yet made for having cured any of these patients. A plea is made to the profession at large to find more cases suitable for this regimen, and to urologists to do this procedure wherever indicated, in order to get enough evidence together to establish or disprove its value. Intensified study of related problems is urged, such as the histopathology of carcinoma of the prostate, hormonal physiology, and the pharmacology of the estrogens.

*1904 Franklin St., Oakland 12, Calif.*

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## WHAT ARE BUCK'S AND COLLES' FASCIAE?

MILEY B. WESSON

Are Buck's and Colles' fasciae surgical designations or anatomical entities? They are of fundamental importance to the urologists because, being closed sacs, they represent the first line of barriers against the spread of urinary extravasation. Some recent publications based on gross dissections and using confusing terminology tend to obfuscation, hence the necessity of this presentation.

Pure anatomists up to fifty years ago were intellectuals living a more or less cloistered life and not interested in the practical application of their dissecting room findings. As a rule, each was an individualist and prone to use original names for structures; consequently the nomenclature was comparable to the well-known tower of Babel. As a result, it became necessary to formulate a uniform set of terms. The world's outstanding anatomists, after a five-year study, met at Basle and promulgated the B.N.A. (Basle nomina anatomica). The Latin designations were to be anglicized, all proper names eliminated, and only descriptive terms to be used.

When I was a first-year medical student, a B.N.A. book, comparable to a dictionary, to correlate the designations used in various books, was a "must." Urologists continued to use the terms, Buck's, Colles' and Denonvilliers' fasciae. These surgical designations, along with that of Gallaudet, are now being used in textbooks of anatomy; but the pure anatomists are not in agreement as to their meaning. Authors who are not familiar with the original writings of Buck and Colles,\* and who get their anatomical knowledge second-hand from various textbooks rather than the operating room, add further to the confusion by misusing the B.N.A. terms. A clear and accurate dissection of the perineum is difficult because of the many fascial layers, the variability in their number, and the occasional fusion of some.

Anatomists should follow the B.N.A. rule of using only descriptive terms and leave to the surgeons the use of proper names for the designation of structures. The dissecting room findings should always be correlated with those of the embryologists, physiologists and the clinicians before publication as authoritative. A hemorrhage into the scrotum that outlines Colles' fascia in purple, is more convincing than a score of drawings or confusing photographs of dissections; furthermore, the personal equation of the dissector and the artist is eliminated.

When I was a student assistant in anatomy, I asked Dr. Franklin P. Mall about Buck's fascia, not mentioned in the textbooks of anatomy, and he replied that such did not exist; it being a surgical designation and not an anatomical entity. The same applied to the recto-urethralis muscle, Colles' and Denonvilliers' fasciae.

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\* Photostatic copies of the original publications were furnished to the audience.

surgeon, I planned to spend a month at Johns Hopkins Hospital. When I went to pay my respects to Dr. Hugh H. Young, he, in his disarming way, suggested that I investigate these fasciae in embryos, and since he said that would take only a few weeks, I agreed. However, all of my spare time for over two years was spent examining the 3000 embryos in the collection of the Carnegie Institute of Embryology; only 32 were old enough to be of any real use. I had many specimens obtained from the autopsy room, and the curator, Dr. George L. Streeter, ordered cut an entire series of pelvises based on the "growth curve." (These slides should be invaluable to investigators because the development of the pelvic structure can be followed. They will be lent to anyone connected with a teaching institution.) I have published pictures of some of the sections and these have been widely copied; whereas pictures of others of the series should, for confirmation, appear in the literature. My study was supplemented with gross dissections of embalmed and fresh cadavers. A series of injections of colored solutions through an endoscope were carried out on recently executed criminals in an attempt to outline both Buck's and Colles' fasciae, but the findings were not consistent and hence, not conclusive.

The term "fascia" is a confusing one. Technically, it is a sheath or band of tissue which invests and connects the muscles. Practically all fasciae are merely compressed layers of the fibrous connective tissue everywhere present, and frequently is split in various ways by different dissectors. My study of serial sections of embryos, stained with differential stains to identify the tissues, showed that fascia is an after-development derived from a condensation of loose mesenchymal tissue. Glass models were made of the serial sections of four embryos. With the aid of an Edinger projection apparatus, the important structures were traced directly on glass plates with Higgins ink of various colors. The glass plates were then stacked, and electric lights were placed behind the model so that there was a three-dimension presentation of the various structures. (Two of these models, made at the University of California, were in the 1940 Golden Gate International Exposition, Western Section, A.U.A. urological exhibit, and the other two are at the Brady Urological Institute, Johns Hopkins Hospital.)

It is universally accepted that the suspensory ligament is an extension of fibers from the fasciae of the *M. rectus abdominis*, the *linea alba* and the pubis that fuses with the dorsal fascia of the penis. It is a triangular shaped plug with the apex beneath the pubis, and its fibers extend backward and fuse with the upper border of the triangular ligament. Scarpa's fascia from above and Colles' from below, are tightly adherent to the anterior layer of the suspensory ligament or base of this wedge shaped mass of fibrous tissue.

An extravasation limited by Colles' fascia first distends the scrotum proper, then the posterior part of the superficial perineal pouch, and finally infiltrates the loose cellular tissues of the pendulous penis outside of Buck's fascia. If there is sufficient pressure, the fluid pushes its way up over the suspensory ligament and beneath Scarpa's fascia. It cannot extend down the thighs because of the attachment of Scarpa's fascia to the *fascia lata*. These findings confirm those of Abraham Colles published in 1811, except that he did not note any extension above the pubic bone.

Twenty-nine years ago, I published a simple diagram of Buck's, Colles' and Denonvilliers' fasciæ, and with slight modifications, it has continued in general use to the present time (fig. 1). The artist misspelled the name Denonvilliers, placing the apostrophe before instead of after the final letter, so my picture was earmarked. Recently its accuracy has been questioned by some pure anatomists because of its practical simplicity. I did not continue leaves of fascia around certain structures since it would have complicated the picture. They all disagree in certain instances as to the nomenclature, and because I made my diagram so simple, they have assumed that I meant things that were not true.

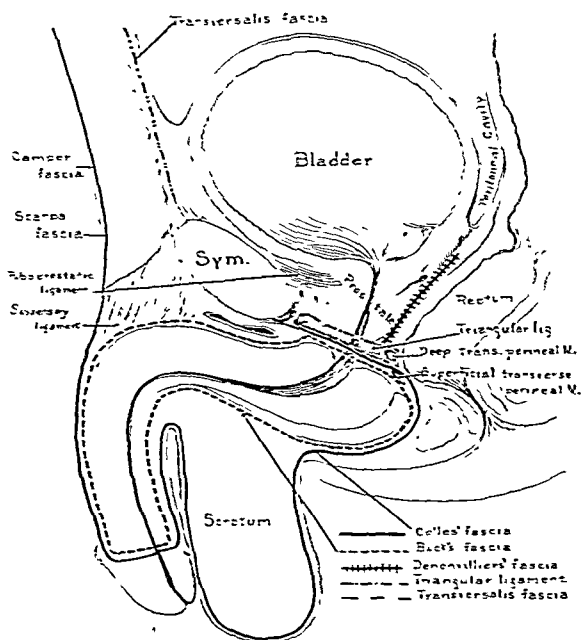


FIG. 1. Perineal fascia

The clinical findings in cases of extravasation of urine, blood and pus, confirm the accuracy of this mid-sagittal view of the fasciæ of the pelvis that I published in 1923 as a working diagram. Time has proved the accuracy of the boundaries of Colles' fascia according to the case reports of Culp, Campbell, Bennardi, Wheeler, Ravenel, Char, and others.

Neither Colles nor Buck described in detail the structures that now bear their names. Buck's fascia is the term commonly applied to a figure of eight fascia, one pocket enclosing the corpus spongiosum and extending from the corona to the anterior layer of the triangular ligament to which it is tightly adherent, and the other, the two corpus cavernosum distal to the crus. Our interest in Buck's fascia is limited to the covering of the corpus spongiosum and that part of corpus cavernosum in close contact with it (i.e., of the penis) The ventral sheath is a complete envelope and will confine within its boundaries an ordinary abscess.

Colles' fascia helps form the anterior layer of the triangular ligament. Posteriorly, it is bounded by the superficial transverse perineal muscle; then, it

passes around the scrotum to the penoscrotal juncture; follows Buck's fascia forward to the corona and then, backward until it becomes lost at the lower edge of the ventral layer of the suspensory ligament. Scarpa's fascia ends nearby at the upper edge. From gross dissection, we know that Scarpa's fascia passes downward from the abdomen over the suspensory ligament and apparently joins Colles' fascia. The juncture with the suspensory ligament is fairly tight, but if there is sufficient extravasation, the fluid can find its way up beneath Scarpa's

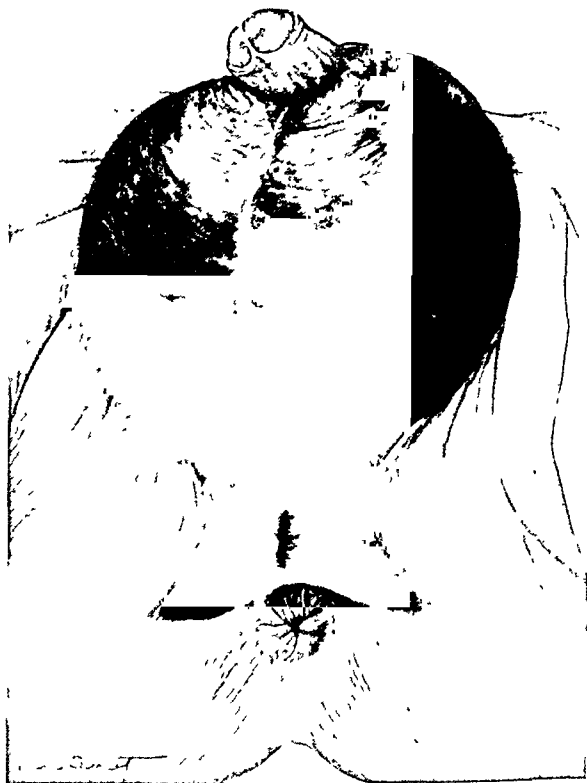


FIG. 2. Colles' fascia in scrotum and perineum outlined by haemorrhage from torn varicocele

fascia. Ordinarily Colles' fascia is a closed sac that incloses the tunica vaginalis of the scrotum and Buck's fascia of the pendulous phallus.

Hemorrhages within the scrotum and abscessed glands of Littre will furnish ocular evidence of the outline of Buck's and Colles' fasciae. Of the former, there are three types of urinary extravasation commonly encountered: 1) between the layers of Buck's fascia; 2) within the superficial perineal interspace; and 3) distal to the deep layer of the urogenital diaphragm. The dorsal sheath of Buck's fascia and the tunica propria of the corpora cavernosa protect these bodies from invasion.

If a rupture of the urethra occurs distal to the urogenital diaphragm, and the tear is ventrally through Buck's fascia, the extravasation of sterile urine or blood

will follow a routine pattern. The extravasation is confined temporarily within the superficial perineal interspace. (Infected urine is a different problem because normal barriers eventually slough, and we have a "periurethral phlegmon".) In the early stages, the extravasation is usually confined to one side of the scrotum. As the tumefaction increases, the extravasated fluid fills both sides of the scrotum, passing from the perineum forward, and into the penis, following Buck's fascia down to the coronary sulcus and then back to the suspensory



FIG. 3. Hemorrhage from tear in corpus spongiosum outlines Colles' fascia of scrotum, phallus and beginning to extend over pubes and beneath Scarpa's fascia.

ligament, and if the pressure is sufficient, the fluid may even pass up beneath Scarpa's fascia on the abdomen as far as the axilla, but cannot spread posteriorly to the ischiorectal fossa and laterally to the thighs.

It is well known that if the rupture occurs proximal to the urogenital diaphragm, the extravasation is held forward and away from the rectum by Denonvilliers' fascia. By dissection up the peritoneum from the bladder, the urine passes into the space of Retzius, and may extend to the diaphragm and eventually through the inguinal rings, and appear on the abdomen.

The first patient whom I saw with Colles' fascia outlined by a hemorrhage had a small tear in a varicocele and the filling was slow, the maximum size not being reached for a week. The discoloration stopped at the lower border of pubes.



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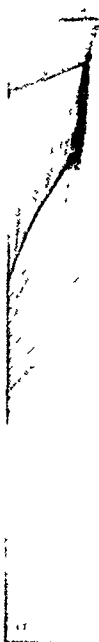


FIG. 2. Colles' fascia and varicocele.

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hot compresses. After the extravasated blood began to absorb, it was found that the shaft of the penis was indurated full length, as there had also been a hemorrhage within the ventral envelope of Buck's fascia. The induration gradually disappeared, and at the end of 2 weeks, the discoloration had faded, but a tender hard circular mass remained in the perineum another 2 weeks. A McCarthy foroblique endoscope was then passed, and a healing linear tear, 1 inch in length was seen in the bulbous urethra about one inch distal from the external sphincter.



FIG 5 Abscess of gland of Littre confined within Buck's fascia

Three cases are reported of localized abscesses, confined by the posterior pocket of Buck's fascia, drained by endoscopic incision and followed by cure, with no stricture formation: The first is a case of circumscribed anaerobic streptococcus abscess within Buck's fascia secondary to a general septicemia; chills and fever, perineal swelling, and bulging mass in the deep bulbar urethra (fig. 4). The second is an abscess of a gland of Littre due to an acute gonorrheal infection and conforming to Buck's original description as a "circumscribed, hard, prominent swelling in the anterior part of the scrotal covering, closely embracing the urethra, and extending on either side around the root of the penis in the form of an indurated, flattened band" (fig. 5). Through an endoscope, a cautery was plunged into the most prominent area, the mass being steadied by the fingers, and a

The penis was distended by the hemorrhage, but the glans which lies outside of Colles' and Buck's fasciae remained pink (fig. 2).

Shortly thereafter, another patient, 48 hours following his third operation for an undescended testicle and a herniotomy, had a venous ooze in the scar tissue. The scrotum was about 6 to 8 inches in diameter and the penis was  $2\frac{1}{2}$  inches in diameter. The discoloration extended to the lower edge of the pubic bone.

Several months ago, a man was referred to me who had suffered a linear rupture of the ventral wall of the urethra and Buck's fascia. The hemorrhage filled

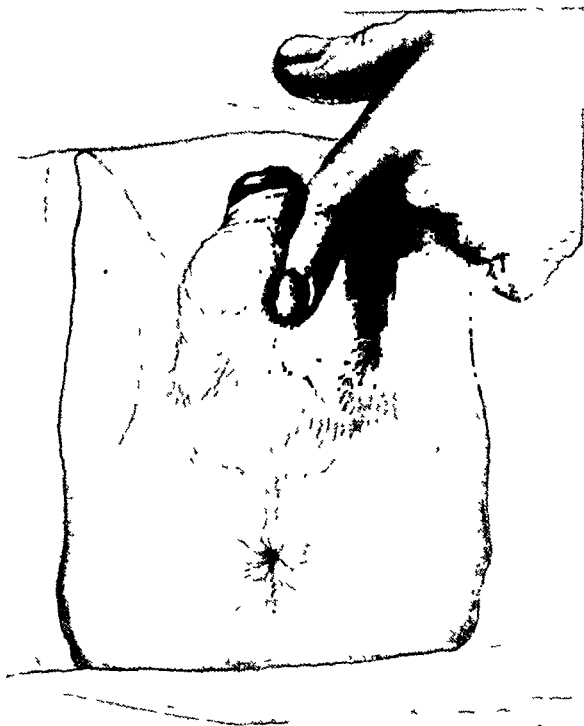


FIG. 4 Abscess within Buck's fascia secondary to a general septicemia

the anterior urethra, posterior envelope of Buck's fascia, Colles' fascia and had started to leak out beneath the attachment of Scarpa's fascia and the suspensory ligament, and up over the pubic bone (fig. 3).

While standing on the sides of an open barrel, the patient slipped and fell straddle of one side. Within an hour, blood was oozing from the meatus. The acute scrotum and phallus were distended and purple from the hemorrhage. Acute retention developed and for 2 days the patient had to be catheterized. When the catheter was first passed, it withdrew blood from the bulbous urethra, but the bladder urine was clear. The hemorrhagic tumor extended from the transverse perineal muscle around to the penoscrotal juncture, up to the coronary sulcus and back to the pubis; and finally, the purple discoloration extended in irregular areas above the upper level of the pubic bone). The only treatment was continual

hot compresses. After the extravasated blood began to absorb, it was found that the shaft of the penis was indurated full length, as there had also been a hemorrhage within the ventral envelope of Buck's fascia. The induration gradually disappeared, and at the end of 2 weeks, the discoloration had faded, but a tender hard circular mass remained in the perineum another 2 weeks. A McCarthy foroblique endoscope was then passed, and a healing linear tear, 1 inch in length was seen in the bulbous urethra about one inch distal from the external sphincter.

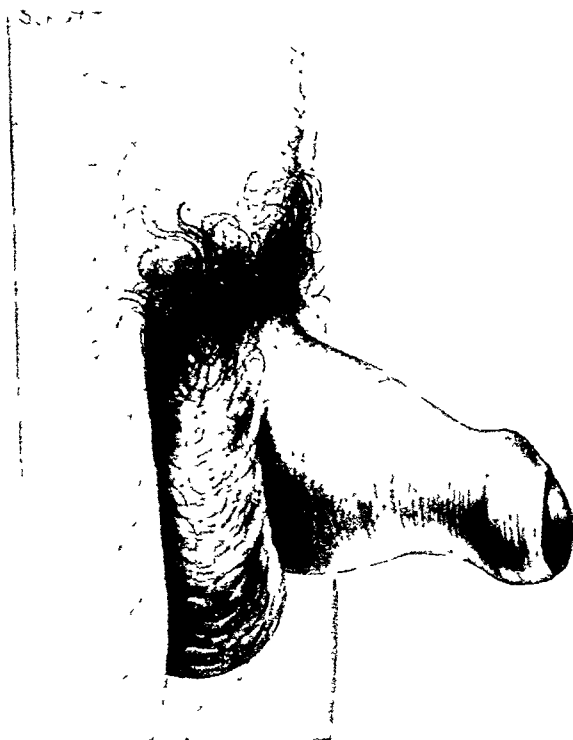


FIG 5. Abscess of gland of Littre confined within Buck's fascia

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large amount of pus was evacuated. Urethral irrigations with an antiseptic solution were used, causing the abscess pouch within Buck's fascia to bulge and when this was squeezed, as if it was the bulb of an asepto syringe, the fluid squirted out a distance of about two feet. In the third case, following excessive stretching of the urethra with a Kohlmann dilator, a mass appeared at the penoscrotal juncture. Two days later, the patient had a temperature of 103F; through an endoscope the circumscribed swelling of the urethra was opened with a cautery and the abscess drained (fig. 6).

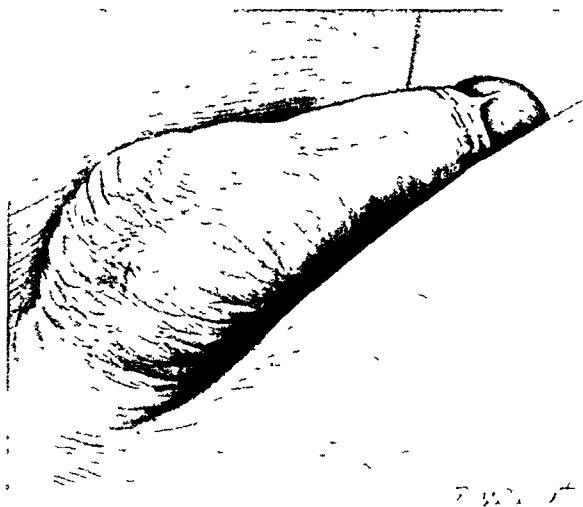


FIG. 6. Extravasation of urine within Buck's fascia due to overdilatation of stricture

#### SUMMARY

The surnames, Buck and Colles, are applied to fascial sacs that control the spread of extravasation of blood and uninfected urine. They have long been considered surgical designations, but some now treat them as true anatomical entities. The structures are not susceptible to a B.N.A. designation, and pure anatomists are not in accord as to the correct names for the component parts.

490 Post St., San Francisco 2, Calif.

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## MULTIPLE PAPILLARY URETHRAL TUMORS SECONDARY TO RENAL PELVIC TUMORS

PHILIP B. POTAMPA

In 1949, I began a paper on renal pelvic tumors with the statement: "Papillary tumors of the renal pelvis have an unusual propensity to involve the ureter and bladder secondarily." I did not include the urethra. Recently an article by Kaplan, McDonald, and Thompson cites 133 cases of papillary tumors of the urinary tract and again no mention is made of secondary involvement of the urethra. Five of our 7 patients with primary tumors of the renal pelvis, seen in the 2 years prior to 1949, had either simultaneous or subsequent *similar tumors* of the ureter, bladder, or both. Since that time I have also removed another kidney and ureter for a papilloma of the lower 2 cm. of the ureter. Numerous observations and reports in the literature attest to the fact that papillomas of the urinary tract are often multiple, but I have found no record of multiple papillomas found in the urethra following the removal of a similar tumor in the kidney. The following case emphasizes the possibility of such a relationship.

### CASE REPORT

C. G., a 61 year old white man, was admitted to the hospital in June 1951, because of recurrent hematuria. It had first occurred in December 1943, when the bleeding was attributed by his doctor to sulfanilamide administered for a cold. When it happened again in May 1945, cystoscopy was performed and the bleeding ascribed to prostatitis, but no pyelograms were made. However, in May 1946, excretory urograms were made because of low back pain, and were described as normal. In November cystoscopy was repeated and retrograde pyelograms made, which disclosed a moth-eaten superior calyx in the left kidney. A nephrectomy was done and the diagnosis established of papillary (epidermoid) carcinoma of the left renal pelvis with invasion of the renal parenchyma.

I had first seen the patient on December 18, 1947 for another episode of bleeding. Cystoscopy at that time had shown a papillary tumor protruding from the left ureteral orifice. The entire remaining ureter, with a cuff of the adjacent bladder, was removed. The specimen was an elongated sausage like tube of tissue containing fluid under some tension and the wall containing several palpable masses. On opening the ureter the masses were found to be from 8 to 30 mm. in diameter, rounded, and covered with a villous papillary epithelium. The microscopic diagnosis was papillary epidermoid carcinoma of the ureter, grade 1.

Cystoscopy 6 months later showed no tumor, but at the end of a year we found a small papilloma on the left lateral wall of the bladder, which was electrocoagulated. He was checked at intervals, but in June 1951, when he was admitted, he had noticed bleeding again. Cystoscopy at this time revealed no tumor in the bladder, but 6 separate papillary tumors were found in the urethra: two in the prostatic portion, and four distal to the external sphincter distributed

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 22, 1952.

along the external urethra almost to the fossa navicularis. These were all thoroughly fulgurated. An excretory urogram showed that the remaining right kidney and ureter were apparently normal. It had been especially noticed that all the urethral tumors were on the left side of the canal. In November 1951, the patient observed further bleeding and on examination we found at least six more papillomas distributed along the left lateral wall of the anterior urethra, two of which were quite large. None was seen in the bladder. All the tumors were again destroyed thoroughly by electrocoagulation through the resectoscope and the panendoscope. The pathological diagnosis again was papillary carcinoma of the urethra. The pyelo-ureterogram on the right was again normal. The patient has not been observed since, but we are anxiously awaiting the opportunity for further examination.

#### DISCUSSION

All papillary tumors of the urinary tract must be considered malignant. However, those of very low degree of malignancy, which some men even call benign, seem more likely to behave in the manner described. Their tendency to recur in the same or another area, to involve multiple sites, and to undergo anaplastic changes justifies this point of view. Moreover, in different parts of one tumor there may be differences in histological structure. When one views the progressive changes which occur in the transitional epithelium of the urinary tract, one can divide these tumors into four groups, according to the classification of McDonald and Priestley. They are 1) papillomas, 2) papillary tumors with infiltration, 3) nonpapillary tumors with infiltration, and 4) epidermoid carcinomas. The prognosis of papillary tumors of the renal pelvis is poor, there being less than 50 per cent 5-year survivals. Six of our 7 cases previously reported are alive at this time.

Explanation of the simultaneous or succeeding involvement with tumor of new areas in the urinary tract has given rise to a great deal of speculation. Three hypotheses as to their pathogenesis have emerged. The first is the theory of surface implantation, or "seeding." The secondary tumors practically always manifest themselves from above downward, in the direction of the urinary current. In our study of the literature on tumors of the renal pelvis prior to 1949 we found no instance of involvement of the ureter or kidney pelvis secondary to a primary tumor of the bladder. However, it is true that we recently removed a kidney and ureter, with a cuff of the bladder, for a papillary tumor of the ureter which was found 2½ years following the transurethral destruction of a single papilloma of the left lateral wall of the bladder. It is difficult to see how broken off fragments of tumor can remain viable and implant themselves on the intact epithelium lower down in the tract or in other areas. This is especially true when the secondary tumors do not appear until 2 or 3 years after the original tumor.

The second theory is that of lymphatic spread. There are strong objections to this, the most obvious being is that the direction of spread is wrong. The lymphatic flow is upward and not downward, while it has already been stated that upward extension from a lesion lower down is distinctly unusual. Moreover,

the tumor appears always to involve the mucosa earliest, when most of them are seen, and the deeper layers only much later. Of course these tumors do grow into the lymphatics. This was shown in one of our previous cases in which the removal of a ureter containing a tumor, with the surrounding cuff of bladder wall, revealed tumor cells in the adjacent lymph channels.

This then leaves the third theory, that of multicentric origin of these tumors, as the most plausible explanation. This is the belief of most observers now, who feel that there must develop a neoplastic tendency in urothelium. This most excellent word has been used to include the epithelial lining of the entire urinary tract. I believe that these urothelial cells are often carcinogenic, or potentially malignant, especially in middle age. This theory is possibly strengthened by the finding that the cancer process, when multiple, often limits itself to that side of the urothelium where it first began. In this case, for instance, the left kidney, left ureter, left wall of the bladder, and left side of the urethra were in turn involved. At no time were any tumors found on the right side. It is my opinion that we can rule out the other theories, and accept the last, the theory of multicentric origin, as the factor in the formation and progression of urothelial tumors.

Since there is no way of preventing such lesions, urologists must do complete cysto-urethroscopic and pyelo-ureterographic studies on every patient who complains of blood in the urine. The complete removal of the initial lesion or group of lesions, in case of neoplasm, does not preclude the possibility of the development of a new growth elsewhere in the urinary tract. Therefore repeated complete examinations must be made on every patient who has had a tumor treated, regardless of its location in the urinary tract, for the remainder of the patient's life. At least no figures have been given so far as to when one can safely stop. The need for such study is not even entirely eliminated after cystectomy, when particular attention must be paid to the urethra, which many of us fail to do. Some of the tumors for which cystectomy has been done have been the more rapidly growing grade 2 papillomas, which have begun to infiltrate. I believe that only the papillomas of grade 1 or 2 ordinarily show this marked tendency to the multiplicity pattern. If properly treated and observed, tumors of this type can probably be controlled very simply as they arise from time to time, with very little distress to the patient.

#### SUMMARY

A case has been presented to suggest that the cells of the urothelium are carcinogenic in certain individuals, and that we can no longer explain multiple urinary tract tumors by the theories of seeding or lymphatic spread. The case report and the discussion indicate that the entire urinary tract, from the kidneys to the urethral meatus, must be investigated both initially and for the adequate follow-up of any papillary tumor or the urothelium.

*610 S. W. Alder St., Portland 5, Ore.*

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## ANASTOMOSIS OF THE VAS DEFERENS TO CORRECT POST VASECTOMY STERILITY

JOHN W. DORSEY

The majority of the medical profession, and a surprising number of urologists, are of the opinion that bilateral vasectomy produces a state of irreversible sterility. O'Connor in 1948 stated that out of 750 urologists who had returned his questionnaire, 615 had never attempted surgical re-union of the vas deferens. It is the purpose of this paper to demonstrate that anastomosis of the vas deferens, or vasorrhaphy, is successful in a sufficiently large percentage of cases as to justify its more frequent performance.

Vasectomy for purposes of sterilization is a relatively safe surgical procedure. Wesson in 1950 thoroughly discussed the legal status of vasectomy as a surgical procedure. As urologists, we should counsel our medical colleagues as to the serious social problems that may be created by the injudicious performance of vasectomy for sterilization, and further emphasize the need for a most careful evaluation of the patient requesting vasectomy.

The reports of successful anastomosis of the vas deferens are limited. Twyman and Nelson, Barker, Nelson, Freiberg and Lepsky, Cameron, and Huffman have reported on single successful cases. O'Connor reported 14 cases of bilateral anastomosis of the vas deferens with a successful result in 9 cases. He also stated that Michelson was successful in 5 cases. Some form of splint was placed in the lumen of the vas in all of the surgical procedures described. Cameron left a hollow steel tube in situ. Michelson utilized two steel wire sutures that were removed in 7 to 9 days. O'Connor used silk-worm gut that was removed in 6 to 10 days. All cases reviewed utilized the end to end technique of anastomosis except the lateral anastomosis of Freiberg and Lepsky.

### CASE REPORTS

*Case 1.* Mr. A. B. S. was 29 years of age. A bilateral vasectomy had been performed 13 years previously at the instigation of his mother in the hope that it would deter him from marrying. This patient married, was divorced, and remarried. Both he and his present wife desired children. A bilateral vasorrhaphy was performed in December 1946. Three weeks postoperative the ejaculate revealed the presence of numerous, well-formed, motile sperm. Two months later the sperm count was 60,000,000 per cubic centimeter. Result considered successful.

*Case 2.* Mr. D. V. J. was 29 years of age. A bilateral vasectomy had been performed 7 years previously at the instigation of his wife who did not desire children. Subsequently the patient was divorced. He remarried and the second wife greatly desired a child. Bilateral vasorrhaphy was performed in March 1947, and viable sperm were present in the ejaculate 18 days later. Conception occurred promptly.

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif., May 22, 1952.

and a baby girl was born 13 months following surgery. Result considered successful.

*Case 3.* Mr. M. F. was aged 29. Due to the ill health of his wife a bilateral vasectomy was performed 6 years previously. The patient subsequently obtained a divorce and was remarried. Both he and his wife desired children. Bilateral vasorrhaphy was performed in February 1950. This patient was followed for 1 year and at no time were sperm observed in the ejaculate. Re-operation in the near future is contemplated. This case must be considered a failure.

*Case 4.* Mr. N. K. A. was aged 32. This couple had two young children, and due to limited finances believed that they could not adequately support more offspring. A bilateral vasectomy was performed 3 years ago, and 1 year later their son had a carcinoma of the adrenal gland and died. One year later a bilateral vasorrhaphy was attempted by his family physician which proved unsuccessful. In July 1950, this patient was operated upon and a bilateral vasorrhaphy performed. Sixteen days following surgery sperm were present in the ejaculate and at 2 months the count was 50 per cent normal. This patient's wife was delivered of a full term baby girl in August 1951. Result considered successful.

*Case 5.* Mr. J. S. was 39 years of age. This couple, following the birth of their second child 9 years ago, felt that they could not afford more offspring. As a result the father submitted to a bilateral vasectomy. One week prior to being seen, their 9 year old son contracted poliomyelitis and died. This couple ardently desired another child, and in December 1950, a bilateral vasorrhaphy was performed. Four weeks following surgery the sperm count was well within the limits of normal. After 6 months of unsuccessful attempts to conceive the wife was examined and the fallopian tubes were found to be obstructed. Result considered successful.

*Case 6.* Mr. F. T. was aged 27. At the request of his wife who did not desire children, this patient submitted to a bilateral vasectomy 6 years ago. He was divorced, remarried, and the second wife desired a child. In June 1951, bilateral vasorrhaphy was performed, and 2 weeks following surgery a few motile sperm were observed in the ejaculate. In the third postoperative month the sperm count was normal, and shortly thereafter his wife conceived, but unfortunately miscarried in the second trimester of pregnancy. Result considered successful.

*Case 7.* Mr. J. D. V. was 25 years of age. This patient had been married 10 months and his wife had failed to conceive. Repeated sperm counts by the attending gynecologist and the author revealed a complete azoospermia. There was no history of previous genito-urinary tract infection. Physical examination revealed a rounded, firm, relatively insensitive induration of the globus minor of the epididymides. The globus major of each epididymis and the vasa did not appear to be involved in the pathological process. A clinical diagnosis of bilateral tuberculous epididymitis was made and the situation fully explained to the patient. With a full knowledge of the possible complications it was his desire that surgery be performed to restore the patency of the genital excretory ducts. On May 10, 1948 a bilateral partial epididymectomy removing the globus minor and most of the body of the epididymis was performed. At the same setting a bilateral epididymo-vasorrhaphy was accomplished. An elliptical incision was

made in the globus major of each epididymis, and the vasa efferentia cut and a milky fluid exuded. The vasa were cut obliquely and a silk-worm suture advanced distally 8 cm. in each vas. The free end was then carried through the wall of the globus major, the dartos, and fixed to the skin of the scrotum. The edges of the vas were approximated to the incision in the globus major with interrupted sutures of 00000 silk. The suture at the distal angle of the vas penetrated only the muscular wall. The incisions healed by primary intention, and the splinting silk-worm sutures were removed on the fifth postoperative day.

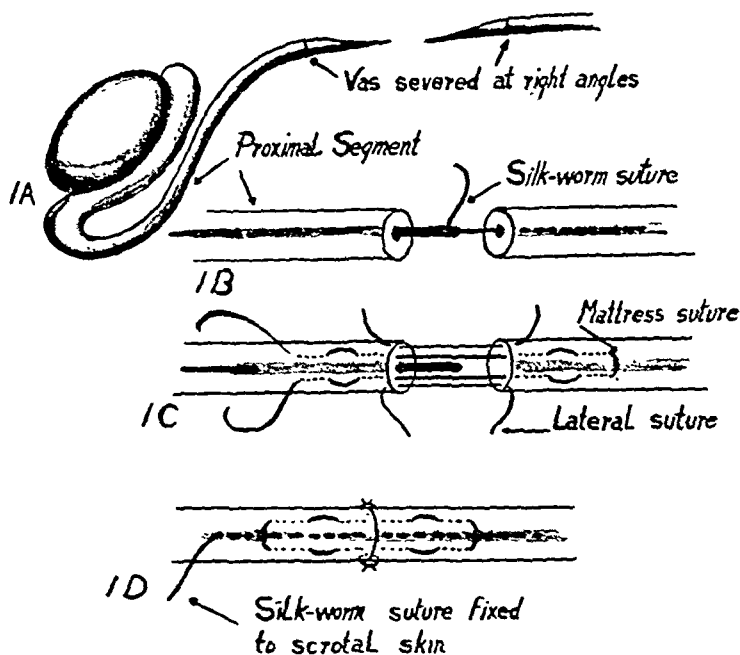


FIG. 1. Schematic illustration of surgical technique. A, vas severed at right angles, B, needle piercing proximal segment of vas C, placement of mattress and lateral sutures D anastomosis completed.

The pathologist reported finding a bilateral tuberculous epididymitis; while sections from the body of the epididymides and vasa were normal. This patient at first exhibited oligospermia, but 8 months later examination of the ejaculate revealed 80,000,000 sperm per cubic centimeter. When last seen this couple were contemplating direct insemination of the husband's semen in an attempt to promote conception.

#### SURGICAL TECHNIQUE

A midscrotal incision 4 to 5 cm. in length is made over the free ends of the vas deferens. The spermatic cord is partially mobilized and the fibrosed ends of the vas are delivered with a minimal amount of dissection in an attempt to preserve the blood supply. Both segments of the vas are severed at right angles above the level of fibrosis, and traction placed on the fibrosed portion while the patency of the lumen is ascertained by the introduction of a strand of silk-worm suture.

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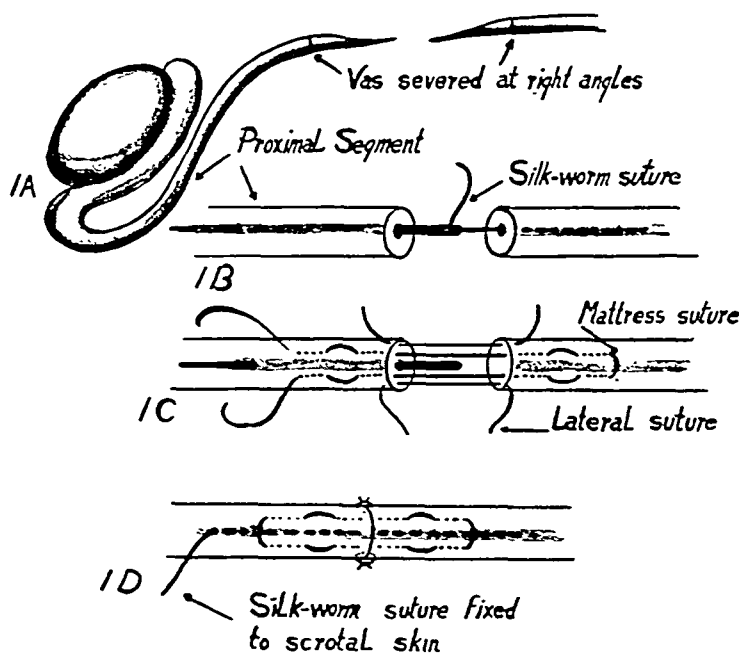


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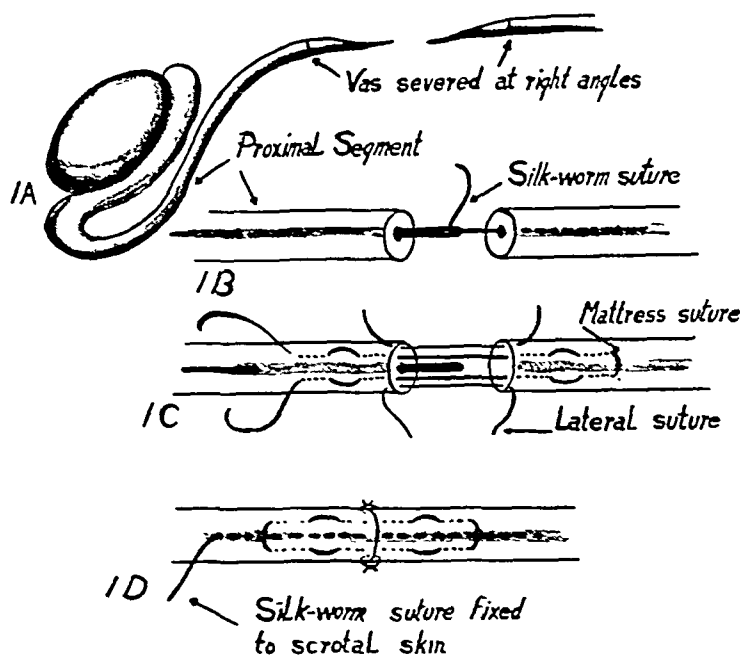


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It is often possible to express a milky fluid from the proximal segment by gentle massage of the epididymis. See figure 1.

A straight round pointed needle, armed with a strand of silk-worm gut, is introduced into the lumen of the proximal segment of the vas toward the testicle and made to pierce its wall at  $1\frac{1}{2}$  cm. (fig. 1, *B*). Then a free end of the silk-worm suture is advanced a distance of 8 to 10 cm. in the distal segment of the vas. The needle is maintained in position to stabilize the vas during the placement of the mattress suture and single lateral sutures (fig. 1, *C*). The mattress suture utilized is similar to that employed by Stoffel in tenoplasty. We believe that this suture co-opts the free ends of the vas with a minimal amount of tension at the line of the anastomosis. In effecting the anastomosis 00000 silk suture is used and care taken not to penetrate the lumen of the vas. Where possible, a second apposing mattress suture is placed in the vas (not illustrated). The single interrupted lateral sutures are primarily for stabilization, while approximation of the anastomosis is maintained by the mattress sutures. The needle is then carried through the wall of the vas, and the scrotal wall, and the silk-worm suture fixed to the skin of the scrotum. No particular effort is made to remove the fibrosed segments of the vas deferens remaining from the previous vasectomy, feeling that further dissection might impair the blood supply at the site of the anastomosis. Where possible the two fibrosed ends of the vas are approximated with a single suture of 000 catgut in an attempt to further relieve any tension at the site of the anastomosis. The fascia of the cord is closed with 000 plain catgut. The scrotal incision is closed without drainage in the majority of cases. The splinting silk-worm sutures are removed between the fourth and sixth days.

#### DISCUSSION

In the cases reported the absence of sperm preoperatively was ascertained both by the referring physician and the author. Testicular biopsy was not performed on the assumption that in these previously fertile patients it might do more harm than good. This impression is confirmed by Henri Bayle, who condemns testicular biopsy, believing that the slight hemorrhage contributes to subsequent fibrosis. It is the concensus of opinion that spermatogenesis is relatively unaffected by obliteration of the vas deferens. Bayle reports finding numerous mobile spermatozoa in three patients with congenital absence of the vas deferens, their respective ages being 41, 36, and 29 years. He also states that operation in genital tuberculosis gave only failure, there being stenosis of the excretory passages and no spermatogenesis in eight (3 per cent). Despite this gloomy prognosis in genital tuberculosis it is apparent that an occasional case will present itself that is amenable to surgical correction, as evidenced by the successful result in case 7. The successful end result in 5 out of 6 cases of bilateral vasorrhaphy is attributed to the method of splinting the anastomosis, the mattress suture for approximating the vas, minimal dissection and gentleness in the handling of tissues.

#### SUMMARY

Sterility following vasectomy was corrected by anastomosis of the vas deferens in better than 80 per cent of cases reported in this series.

A previous unsuccessful attempt at vasorrhaphy is not a contra-indication to re-operation.

Testicular biopsy preliminary to vasorrhaphy was not performed in this series of cases.

Surgical occlusion of the vas does not appear to abolish spermatogenesis. Normal sperm were observed in one of our patients thirteen years following vasectomy.

Epididymo-vasorrhaphy should be attempted more frequently following partial epididymectomy in an attempt to preserve the fertility of the male.

*125 E. 8th St., Long Beach, Calif.*

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## PRIMARY RETROPERITONEAL TERATOMA

RICHARD CHUTE, SAMUEL E. LEARD AND RUDOLF OSGOOD

*From the Massachusetts Memorial Hospitals and the Boston University School of Medicine, Boston, Mass.*

A comprehensive review of this subject by Palumbo and his coworkers<sup>1</sup> published in 1949 reveals that, although about 500 primary retroperitoneal tumors—mostly sarcomas—have been reported in the world literature, only about 10 per cent of these have been teratomas, of which only 58 cases had been reported up to that time. Since then, one more case was reported by Baker and Ragins<sup>2</sup> in 1950. Therefore because of the rarity of this condition, and because pyelography is of the greatest importance in making the diagnosis of retroperitoneal tumors, due to their close proximity to the kidney and ureter, it seems worthwhile to discuss this subject before this urological group and present a case of this condition.

In considering these tumors, the retroperitoneal area is taken to be the region between the posterior parietal peritoneum and the posterior body wall. It is bounded above by the diaphragm and below by the pelvic diaphragm. In addition to the kidneys, adrenals, pancreas, and the posterior surface of portions of the intestine, the retroperitoneal space also contains blood vessels as the aorta and the inferior vena cava, with many branches and tributaries respectively, lymphatics, nerves, and areolar tissue. By the term "primary" it is meant that the tumors under discussion arise independently from tissue in the retroperitoneal region, notably the embryologic urogenital cell ridge, and not from adjacent organs such as pancreas, adrenal, or kidney. Also malignant metastases, which are quite common in this region, are excluded from this discussion.

As regards the details of the origin of these primary tumors, there is no general unanimity of opinion, but there is agreement that they are of congenital nature and arise from embryonic pluri-potential cells, and also that their growth is not under the orderly control mechanism governing normal tissues, so that they may grow in an uncontrolled and disorderly manner, and may become dangerous malignant tumors. During their development they may push any of the abdominal viscera away from the posterior abdominal wall. Also they may grow into the mesentery of the large or small bowel and may extend downward over the promontory of the sacrum into the pelvis. They may be solid or cystic, but are usually a combination of both.

Teratomas may grow to a very large size; the largest one on record weighed 26 pounds. They have been found twice as frequently on the left side as on the right, and are slightly more common in females. As is to be expected from their congenital nature, they tend to manifest themselves in the younger age groups.

Read at meeting of New England Section of the American Urological Association, Boston, Mass., February 21, 1952.

<sup>1</sup> Palumbo, L. T., Cross, K. R., Smith, A. N. and Baronas, A. A.: Primary teratomas of the lateral retroperitoneal spaces. *Surgery*, 26: 149, 1949.

<sup>2</sup> Baker, W. J. and Ragins, A. B.: Pararenal teratoma: Case report. *J. Urol.*, 63: 982, 1950.

Palumbo et al. found 55 per cent in the first decade, 35 per cent in the second and third decades, and only 10 per cent after the age of 30.

Symptoms as a rule are the result of pressure on various structures by the growing neoplasm. At first the symptoms are vague, although persistent, and are apt to consist of mild abdominal discomfort with anorexia, eructations, heartburn, and constipation or diarrhea, which may baffle the diagnostic ability of the physician. A persistent low-grade swinging fever, the cause of which is not obvious, may occur. Later, as the tumor mass increases in size, there are apt to be symptoms of partial intestinal obstruction with more marked constipation or diarrhea, crampy pains, increasing anorexia, and even nausea and vomiting. Back pain may be bothersome. Prominence and dilatation of the veins of the anterior abdominal wall occur sometimes, as does edema of the legs. Loss of weight and strength is usual.

As the lesion develops, an abdominal mass can usually be palpated, and the question arises as to its nature. Even if a mass cannot be felt, the symptoms commonly lead to the taking of gastro-intestinal x-rays. If the mass is large, the ascending or the descending colon may be markedly displaced from its normal position. The chief value of the gastro-intestinal x-rays in these cases is to exclude that tract as the primary site of the tumor. If the gastro-intestinal tract has been eliminated as the primary site, urography is indicated and almost always gives very valuable information, as practically all retroperitoneal tumors, as they enlarge, exert some pressure on the ureter or the kidney, and thus reveal their presence and position. Commonly these tumors press upon the ureter and/or the kidney from the rear, pushing them forward and laterally, and sometimes obstructing them. This is true not only of teratomas, but also of retroperitoneal tumors of every type. The x-ray cannot differentiate between teratomas and other retroperitoneal tumors, unless bones, teeth, or calcific deposits are revealed within the tumor. Frequently on account of pressure on and resulting obstruction of the upper urinary tract by these tumors, the intravenous dye is not excreted well and retrograde pyelograms may be necessary for satisfactory delineation. The urograms should be taken not only in the usual anterior-posterior view but also in the oblique or lateral view. Schulte and Emmett<sup>3</sup> have pointed out that it is very rare for tumors or cysts of the pancreas—no matter how large—to displace the kidney or ureter. This is an important diagnostic point.

What are the characteristic changes in the urogram produced by retroperitoneal tumors? Most frequently the kidney and upper ureter on one side are definitely displaced laterally and anteriorly; although medial displacement can occur. Sometimes the kidney is displaced upwards, and its lower pole pushed more laterally than usual. Rarely the kidney is displaced downwards, but great care must be taken to distinguish this from renal ptosis. Sometimes the kidney is rotated to a greater or less degree. There may be obstruction at the ureteropelvic junction, and occasionally the upper or middle ureter is obstructed with dilatation above. Usually a large, soft tissue mass producing the displacement and obliteration.

<sup>3</sup> Schulte, T. L. and Emmett, J. L.: Urography in the differential diagnosis of retroperitoneal tumors. *J. Urol.*, 42: 215, 1939.

ing the psoas shadow can be seen in the x-ray picture, but this is not always the case. Retroperitoneal pneumography may well prove to be of value in the delineation of these tumors, but no reference to its use in such cases has been found.

The ideal treatment of retroperitoneal teratomas is complete surgical excision, including as wide a margin of safety of uninvolved tissue as possible. Unfortunately, however, when the teratomas are malignant, they frequently are found to be so advanced and to have involved vital structures to such an extent that their total removal is quite impossible. When this is the case, and also in cases where they have been removed but were frankly malignant, x-ray therapy has been shown to usually be of some benefit. While this obviously cannot affect the most adult portions of the tumor, it may help destroy the more susceptible portions.

In Palumbo's series at least 10 per cent of the teratomas were frankly malignant at the time of operation. A good many others, even though no definite microscopic evidence of malignancy was found, behaved in a malignant manner and were prone to recur and even to metastasize to liver, lungs, and vertebrae. Therefore in general the prognosis at best is guarded and uncertain.

#### CASE REPORT

R. G., a 44-year old white married shipyard worker, was admitted to the Massachusetts Memorial Hospitals. His past history was non-contributory. Seven weeks previous to entry he had the sudden onset of severe steady pain in the back and lower mid-abdomen which caused him to double up and to take to his bed. There was no nausea or vomiting. The next day his physician saw him and, since he was still in pain and had a fever of 101F, gave him morphine and penicillin. When he still had fever and pain after 4 days, he was admitted to a hospital in his home town, and sedatives and penicillin continued. Retrograde pyelograms were performed which were said to be normal. After 10 days the pain and fever gradually subsided, and he left the hospital. After recuperating at home for some weeks, he went back to work for a few days but did not feel very well, and 2 weeks before entry had recurrence of pain with a shaking chill. Again he was hospitalized and given penicillin. A barium enema was performed and reported as negative. It was noted that whenever he had an enema his pain became worse. His physician, baffled by the situation, referred him to the Massachusetts Memorial Hospitals. Physical examination on entry was not remarkable. He was in no great distress. No masses were felt in the abdomen, but there was some tenderness below the umbilicus. Breasts and prostate felt normal. Testes were small normal. Laboratory examinations including urinalysis, urine culture, complete blood count, nonprotein nitrogen, icterus index, stool examination, etc., were all normal. The sedimentation rate was slightly elevated (27 mm. in one hour). A plain x-ray film of the abdomen showed the psoas shadows distinct, and no masses were visualized. Chest x-ray was normal. Excretory urography (fig. 1, A) showed a normal right kidney and ureter, except for some lateral deviation of the ureter opposite the fourth lumbar vertebra. On the left side the lower pole

of the kidney was displaced laterally somewhat. Also the dye was slow to appear in this kidney, and all calyces were markedly dilated and blunted, suggesting some obstruction. Retrograde (fig. 1, *B*) pyelograms confirmed this finding, and also revealed some rotation of this left kidney, and lateral displacement of the



FIG. 1. *A*, 20 minutes excretory urogram showing peculiar dilatation of all calyces of left kidney and also lateral displacement of right ureter opposite fourth lumbar vertebra. No shadow of mass is seen. *B*, retrograde pyelogram showing left upper ureter and lower pole of left kidney pushed laterally. Note some rotation of kidney. *C*, film taken 80 minutes after retrograde pyelogram. Note delayed emptying of left kidney. Dye still present in pelvis.

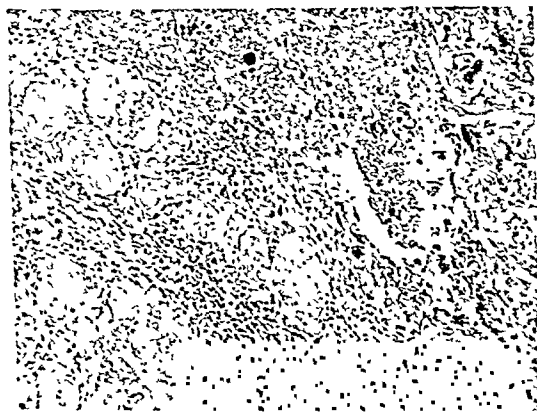


FIG. 2. Groups of anaplastic epithelial cells interspaced in more abundant sarcomatous type of tissue. Also syncytiotrophoblasts and cytotrophoblasts.

left upper ureter. After the catheter through which the dye had been introduced had been withdrawn from the kidney pelvis, the pelvis was very slow to empty, and an x-ray taken one hour and twenty minutes afterward showed plenty of dye still in the left kidney pelvis (fig. 1, *C*). He was operated upon with the diagnosis of ueteropelvic obstruction, the nature of which was not clear. At operation a normal kidney was encountered, whose pedicle and pelvis were being pushed



laterally and anteriorly by a cystic mass considerably larger than a golf ball, which was behind and medial to the kidney. It was seen that pressure from this caused the poor emptying of the kidney and the hydronephrosis. The abdomen was explored, and it was found that this cystic mass was at the upper end of a firm, fixed mass, as large as a good-sized cucumber, which ran downward and medially and which eventually invaded and fused with the left psoas muscle at about the level of the bifurcation of the aorta, which it partially covered. On the right side, at about the same level, a hard, fixed nodule the size of a hen's egg protruded from the right psoas muscle. It was quite obvious that the tumor was

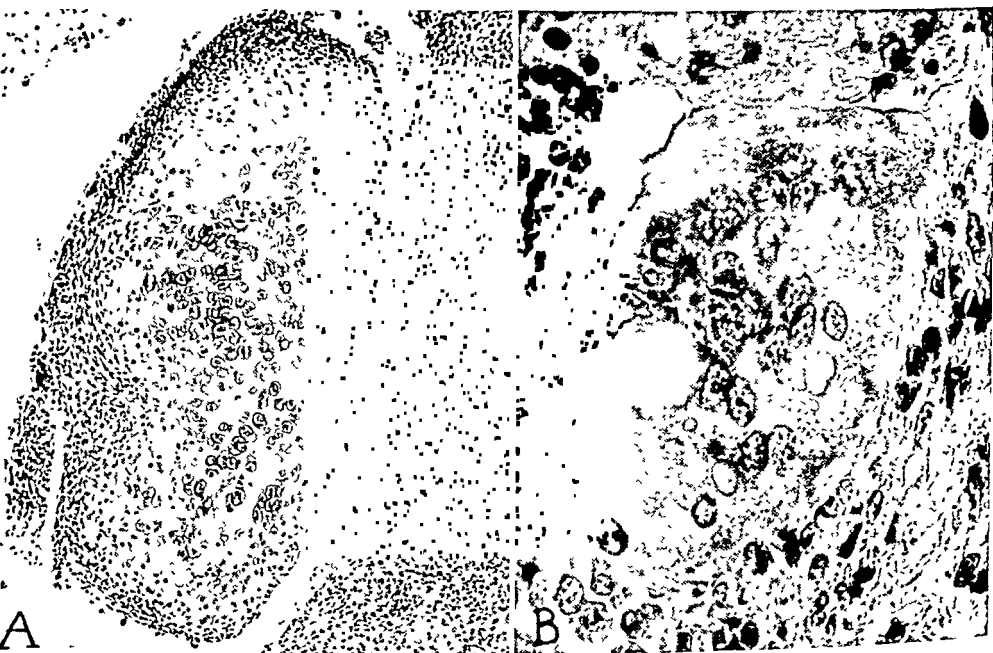


FIG. 3. *A*, island of chondrosarcoma as component of malignant teratoma. *B*, tumor giant cell surrounded by fibrosarcomatous tissue.

inoperable, and therefore a generous biopsy was taken from the junction of the cyst and the body of the tumor, and the wound was closed.

Gross examination of the tissue removed at biopsy showed it to be pinkish-yellow, mushy, friable, and in places necrotic. Microscopic sections showed an undifferentiated malignant tumor composed of anaplastic carcinomatous and sarcomatous tissue, with areas of characteristic choriocarcinoma and of chondrosarcoma. The diagnosis was primary malignant teratoma (figs. 2 and 3).

The patient made a very satisfactory convalescence, following which he was given a total of 4,800 roentgen units of 200 KV x-ray therapy to the region of his tumor during the next 2 months. He did well for 4 months after the completion of this x-ray therapy, but then began to complain of pain in the right lower abdomen in a region corresponding to the position of the egg-sized nodule projecting from the right psoas muscle. A mass could be felt there, and during the

course of the next two months, 10,000 units of 200 KV x-ray therapy were given to this mass and also elsewhere in the abdomen through several portals. This gave relief of his symptoms for two months, but then he began to complain of severe back pain, and to have persistent and intractable vomiting. He went downhill rapidly, became emaciated, and died in his home town nine and one-half months after aoperation

#### SUMMARY

A case of primary retroperitoneal teratoma is reported, and this rare malignant condition is discussed.

Symptoms are the result of pressure on various structures by the growing neoplasm. Early symptoms are vague but persistent abdominal complaints, while later symptoms are abdominal or back pain often accompanied by symptoms of partial intestinal obstruction, and by deterioration in general condition.

In most cases a mass is eventually discovered on physical examination, although none was detected pre-operatively in the case reported.

Urography is invaluable in the diagnosis of retroperitoneal tumors, which usually displace the kidney or ureter laterally and anteriorly, sometimes upwards, and may obstruct them. This occurred in the case reported.

The ideal treatment is complete surgical excision, but these tumors are often inoperable, and in general the prognosis is poor. X-ray therapy may give some palliation.

# AORTOGRAPHY AND RETROPERITONEAL OXYGEN IN UROLOGIC DIAGNOSIS: A COMPARISON OF TRANSLUMBAR AND PERCUTANEOUS FEMORAL METHODS OF AORTOGRAPHY

ROBERT C. WALTER AND WILLARD E. GOODWIN

*From The Department of Surgery, Urology, Wadsworth Veterans Administration Hospital and the University of California, School of Medicine, Los Angeles*

Aortography has provided the urologist with a diagnostic technique of recognized value for investigation of pathologic conditions of the kidneys and retroperitoneum and of the aorta and its branches.<sup>1-7</sup> Increasing experience in application of this form of diagnosis has led to modifications of technique which are worthy of mention. A previous publication<sup>8</sup> described and compared aortography by translumbar aortic puncture and by retrograde catheterization of the aorta through surgical exposure of the femoral artery. It was concluded that "translumbar needle aortography was simpler and less hazardous and should be the method of choice in all suitable cases." Peirce's subsequent development of the simpler technique of percutaneous catheterization of the femoral artery:<sup>9,10</sup> has led to need for further comparative study of the two methods.

It is the purpose of this paper to examine techniques currently employed in translumbar and percutaneous femoral artery catheterization aortography and to enumerate the advantages of, and indications for, each. In addition, the use of retroperitoneal oxygen insufflation as a useful adjunct to aortography in selected cases is reported.

## METHODS

*Translumbar aortic puncture.* The basic technique of translumbar aortic puncture as originally advocated by Dos Santos and since described in detail by others<sup>11, 12, 13</sup> has been used (fig. 1). In the past we have used pentothal sodium or spinal anesthesia, but recently we have been well satisfied with local infiltration anesthesia.<sup>14</sup> After adequate premedication, 1 per cent procaine solution is infiltrated to a depth of two inches at the point selected for insertion of the aortography needle. The remainder of the procaine required is injected through the needle employed for aortic puncture as it is advanced slowly along the

Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif. May 22, 1952.

<sup>1</sup> Editorial J. A. M. A., 148: 652, 1952.

<sup>2</sup> Life, February 25, 1952, p. 129.

<sup>3</sup> Leriche, R., Beaconsfield, P. and Boley, C. Surg., Gynec. and Obst., 94: 83, 1952

<sup>4</sup> Griffiths, I. H. Brit J Urol, 22: 281, 1950.

<sup>5</sup> Nelson, O. A. J. Urol, 53: 521, 1945

<sup>6</sup> Doss, A. K. J. Urol, 55: 594, 1946

<sup>7</sup> Smith, P. G., Rush, T. W. and Evans, A. T. J. Urol, 65: 911, 1951

<sup>8</sup> Goodwin, W. E., Scardino, P. L. and Scott, W. W.: Ann. Surg, 132: 944, 1950

<sup>9</sup> Peirce, E. C., II Surg, Gynec. and Obst, 93: 56, 1951.

<sup>10</sup> Abeshouse, B. S., Scherlis, I., Golden, M. and Rubin, M.: Urol and Cutan Rev, 55: 517, 1951

<sup>11</sup> Wagner, F. B., Jr. J. Urol, 56: 625, 1946

<sup>12</sup> Melick, W. F. and Vitt, A. E. J. Urol, 60: 321, 1948

<sup>13</sup> Smith, P. G., Rush, T. W. and Evans, A. T. J. A. M. A., 148: 255, 1952

<sup>14</sup> Detering, R. A., Jr. Surgery, 31: 88, 1952

translumbar route. Most patients experience discomfort as the needle tip reaches the vertebral body, but this is readily controlled by injecting more procaine at this point. Another injection is made as the needle tip approaches the aorta. A total of 10-20 cc of 1 per cent procaine is all that is ordinarily required. When local anesthesia is used, the patient may, after injection of any contrast medium, note brief cramping abdominal pain or a sensation of warmth. This also occurs in aortography by percutaneous femoral artery catheterization using local anesthesia and is not entirely obviated by spinal anesthesia. It is our impression that intra-aortic injection of 5 cc of 1 per cent procaine<sup>15</sup> immediately preceding injection of the contrast material reduces abdominal discomfort. No ill effects from this technique have been noted to date. Most patients report that translumbar

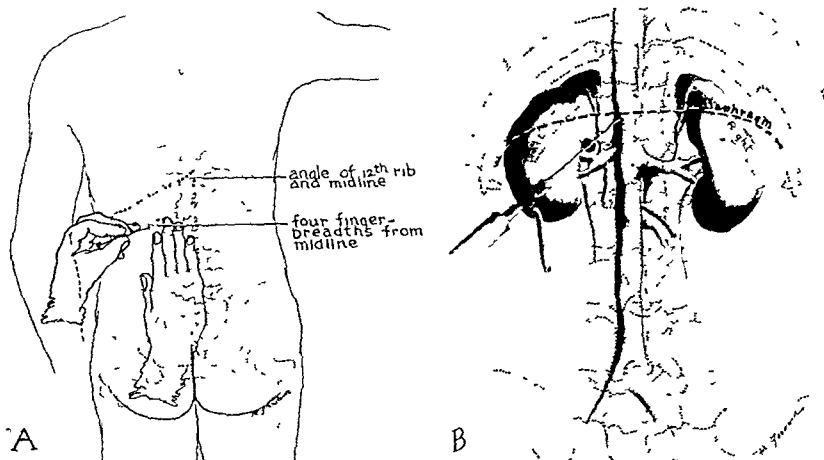


FIG 1 A, landmarks for translumbar aortic puncture four fingerbreadths to left of midline below twelfth rib Patient in prone position B, approximate site of aortic puncture.

aortography under local anesthesia is less disturbing than cystoscopy. The needle we have used to best advantage for translumbar aortic puncture was designed especially for aortography.\* It is a 17 gauge, 7 inch steel needle of special thin wall tubing which has the inside diameter of a 16 gauge needle. It has a modified Huber point which provides some directional control of the flow of contrast medium as it leaves the needle tip (fig. 2, A). The jet of fluid produced by forceful injection leaves the needle at an angle (fig. 2, B). This has been helpful in directing the contrast medium cephalad and dorsally away from the superior mesenteric artery or toward the left or right renal artery as desired. The large bore of the needle permits a rapid and effective injection. A needle stop is a useful addition to equipment for translumbar aortic puncture. It is a small metal cylinder bored to thread easily on the needle shaft and has a setscrew for fixing its position (fig. 2, A). When the aortic puncture needle is properly placed, the needle stop is placed against the patient's back and set on the shaft. This pre-

<sup>15</sup> Graubard, D. J. and Peterson, M. C. *Clinical Uses of Intravenous Procaine*. Springfield, Ill. Charles C. Thomas, 1950

\* B-D \* T166, LNR11 17 gauge 7" needle with Huber point. Furnished by Oscar Schwidetzky, Becton, Dickinson Company, Rutherford, N. J. (The use of this type of needle was first suggested to us by Dr. Converse Peirce in May 1950.)

vents the needle from entering further or indicates outward displacement during subsequent manipulations.

All injections have been made by hand using a 10 cc Luer-lok syringe with metal finger and thumb rings. The syringe is most conveniently adapted to the needle by a one foot length of transparent plastic tubing with Luer-lok attachments and a stopcock.<sup>7</sup>

*Percutaneous femoral artery catheterization.* Peirce's method<sup>9</sup> of percutaneous femoral artery catheterization aortography has been followed in this study (fig. 3). This procedure is usually carried out using adequate premedication and local infiltration anesthesia with 1 per cent procaine at the site of puncture in

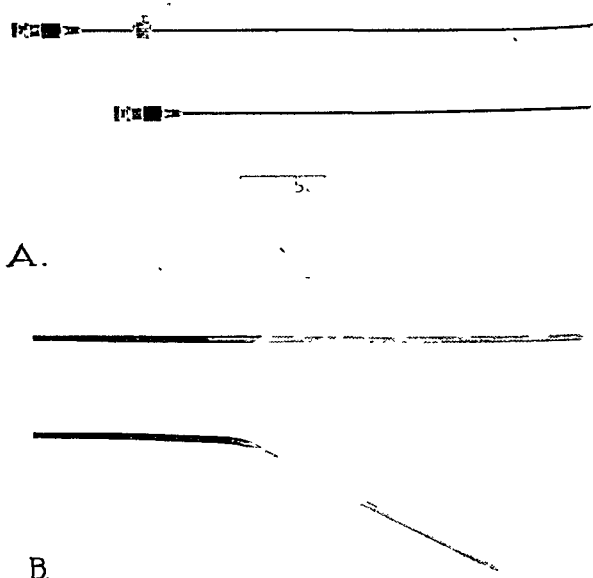


FIG. 2. A, special Huber point needle with needle-stop on shaft (above), and conventional needle; B, jet of fluid produced by injection of conventional needle (above) compared with injection of Huber point needle.

the femoral artery just below the inguinal ligament. If general anesthesia is employed, local infiltration of procaine at the site of puncture is used to prevent arterial spasm. Originally we used a short bevel, 13 gauge, 4 inch needle for arterial puncture and introduction of the polyethylene tubing. Recently we have used a 12 gauge Robb cannula\* which accepts a larger tubing† that has an outside diameter of 0.075 inch and an inside diameter of 0.055 inch. After the tubing has been advanced into the aorta the cannula is withdrawn from the artery to prevent shearing of the tubing. Steady pressure is applied over the puncture site to prevent hemorrhage. The distal end of the tubing is fitted with a blunt-end 15 or 16 gauge needle and stopcock to permit easy intermittent injection of contrast medium.

*Test injection of contrast medium.* In aortography by either method it is our

\* B-D No. 485 LNR 12 gauge 2" special needle for percutaneous femoral aortography.  
 † Supplied by Medical Plastics, Inc., 4512 Marble Hall Road, Baltimore 12, Md.

practice to use a test injection of 3-4 cc of contrast medium followed by immediate x-ray exposure. This "scout film" is evaluated before further injections are made. After translumbar puncture and injection using the Huber point needle, enough detail is obtained to indicate the need for rotation of the needle to prevent excessive filling of the superior mesenteric artery or to direct the stream of contrast material to one side or the other. In a case in which the test dose produced epigastric pain, nausea, and vomiting, the "scout" x-ray film showed that the superior mesenteric artery had received most of the contrast material. The needle tip was rotated accordingly, and subsequent injection of 12 cc of contrast medium produced no discomfort or nausea and little filling of the



FIG 3 Peirce's method of percutaneous femoral artery catheterization. A, 12 gauge Robb cannula; B, tubing advanced through cannula following femoral artery puncture; C, course of tubing from puncture site to abdominal aorta.

superior mesenteric artery. A test injection and "scout" x-ray also decrease the likelihood of extravasation of a large amount of contrast medium in the translumbar method.

The test injection utilized with the percutaneous femoral method visualizes the course of the polyethylene tubing, which is non-opaque, and indicates the position of its tip in relation to the structures of primary interest. The tubing may then be adjusted upward or downward to secure maximal filling of the desired area with the final injection.

Each injection of contrast material is followed by an injection of 10-20 cc of normal saline solution which clears the needle and tubing of the contrast medium and blood. We have not found the use of heparin necessary.

*Contrast media.* Sodium iodide solution was not employed in this study as earlier observations showed it to be too irritating.<sup>5</sup> We have utilized 75 per cent neo-iopax, 70 per cent urokon,\* and 70 per cent diodrast. Diodrast though sufficiently opaque is less desirable because of its viscosity and tendency toward

\* Supplied by Melvin A. Thorpe, Mallinckrodt Chemical Works, St. Louis, Mo.

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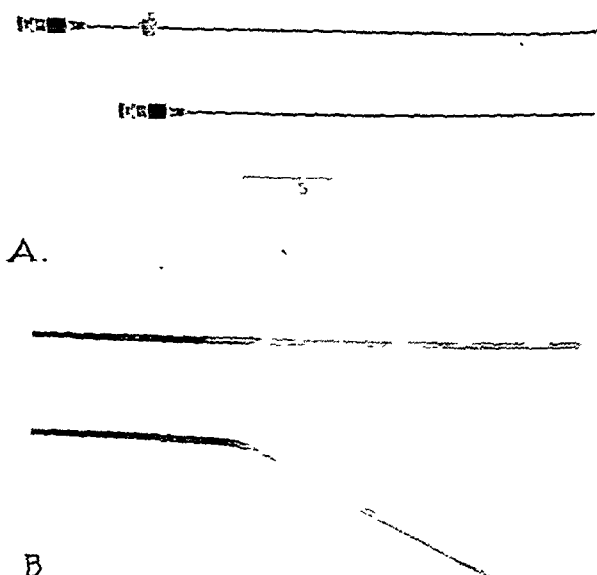


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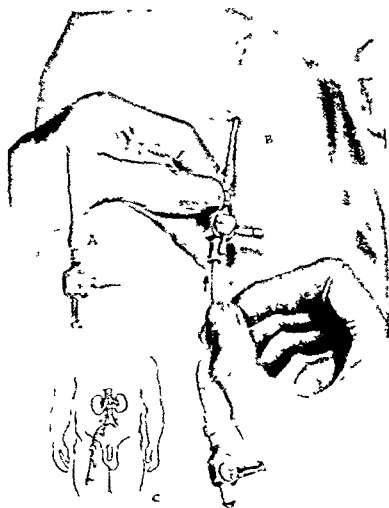


FIG 3 Peirce's method of percutaneous femoral artery catheterization. A, 12 gauge Robb cannula, B, tubing advanced through cannula following femoral artery puncture; C, course of tubing from puncture site to abdominal aorta.

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crystallization when cooled or exposed to air. Both 75 per cent neo-iopax and 70 per cent urokon provide excellent arteriograms of similar contrast quality. They are equally well tolerated and neither one produces undue pain when injected into the aorta under local anesthesia. At present we have no established preference for one or the other.

After the test injection, 10–12 cc of contrast medium is rapidly injected for the aortogram. Often 10–12 cc suffices for a diagnostic arteriogram, but we do not hesitate to repeat the procedure or use a 20 cc injection if necessary to produce desired results. Later films usually show an excretory urogram which is often helpful in conjunction with subsequent aortograms. On occasion we have used 120 cc of 75 per cent neo-iopax in a single patient during one examination with-

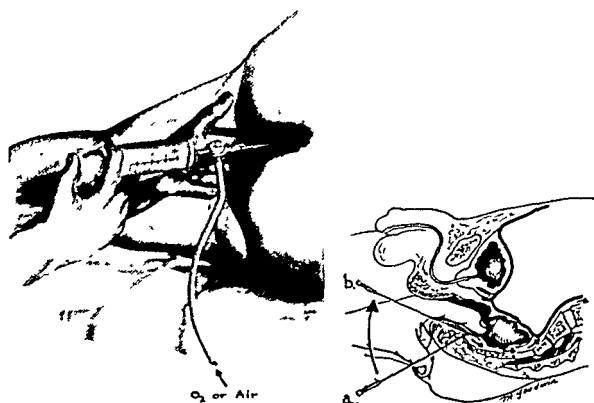


FIG. 4. Presacral injection of oxygen for retroperitoneal pneumography (Rivas). Needle tip lies in loose areolar tissue between rectum and sacrum.

out apparent ill effect. However, in cases where more than two or three injections have been made, diffuse clouding with loss of detail has been apparent on the x-ray films. This effect is apparently the result of tissue opacification, particularly noticeable in the liver and spleen. In none of the recent cases was evidence of iodism or intolerance to the contrast medium noted. In a larger series observed by one of us, there were two instances of acute iodism, neither of which was serious.

*X-ray technique.* In aortography by either technique we have most often employed a single x-ray exposure timed to coincide with injection of the last cc of contrast material. The x-ray examination is conducted on an ordinary radiographic table equipped with a Buckey grid and an overhead 200 MA tube with rotating anode. The patient is in a prone position during translumbar aortography and supine during percutaneous femoral aortography. Blurring due to motion is prevented by an exposure time of  $\frac{1}{10}$  to  $\frac{1}{15}$  second. Other factors are a 36 inch tube film distance; an 80–95 kilovoltage, and 13 MAS.

Effective use of rapid cassette-changing devices for multiple exposure during the course of a single injection has been described elsewhere.<sup>16, 17, 18</sup> In some

<sup>16</sup> Goodwin, W. E., Sloan, R. D. and Scott, W. W.: *J. Urol.*, **61**: 1010, 1949.

<sup>17</sup> Blum, E., Witz, J. and Gandar, R.: *J. d'urol.*, **57**: 387, 1951.

<sup>18</sup> Melick, W. F., Yarbrough, G. P. and Boler, T. D.: *J. Urol.*, **65**: 45S, 1951.

cases in the present study this technique has been used to good advantage (fig. 12). A Sanchez-Perez seriograph is used. Best results are obtained when eight films are exposed in 4 seconds. The first film is exposed before injection is begun. Rapid injection occupies films 2, 3, and 4, and the remainder of the films show a late phase giving good nephrograms and delineating tumors. This method of x-ray exposure practically assures a good arteriogram since the problem of synchronization of injection and x-ray is removed. Serial films may produce a combination of details impossible to achieve by any other means. Utilization of a rapid cassette-changing device, particularly in renal arteriography, significantly enhances the diagnostic acuity of the procedure.



FIG. 5. Saccular aneurysm of abdominal aorta demonstrated by percutaneous femoral method of aortography.

We have in the past tried the Valsalva maneuver or tourniquets on the lower extremities to impede dispersion of the contrast medium without demonstrable improvement in results. These techniques were not used in the present study.

*Retroperitoneal oxygen insufflation.* Retroperitoneal pneumography, devised by Rivas,<sup>19</sup> and more recently advocated by Smith et al.<sup>20</sup> is a definite aid to visualization of retroperitoneal structures. The ease with which it can be accomplished, the lack of discomfort on the part of the patient, and additional diagnostic information obtained recommend its use. We have used it most frequently in cases with retroperitoneal tumors, especially those of the kidneys. These same cases are often subjects for aortography. When retroperitoneal insufflation of oxygen is completed, approximately 30 minutes before aortography, sufficient diffusion in the perirenal areas will have occurred. When the lesion is unilateral, insufflation may be directed to the side in question by placing the patient as for administration of spinal anesthesia with the affected side uppermost. If bilateral insufflation is desired, the patient may be turned from side to

<sup>19</sup> Rivas, R. M.: *Am. J. Roentgenol.*, 64: 723, 1950.

<sup>20</sup> Smith, Donald R., Steinbach, H. L., Lyon, R. P. and Stratte, P. B.: *J. Urol.*, 68: 953, 1952.

side or placed in the prone, knee-chest or lithotomy position during oxygen injection.

Using local infiltration anesthesia a 19 or 20 gauge, 4 inch spinal needle is introduced through the skin and subcutaneous tissue beside or beneath the tip



FIG. 6. Translumbal aortogram indicating arteriosclerotic obliteration of abdominal aorta just below renal arteries. Note extensive collateral circulation.

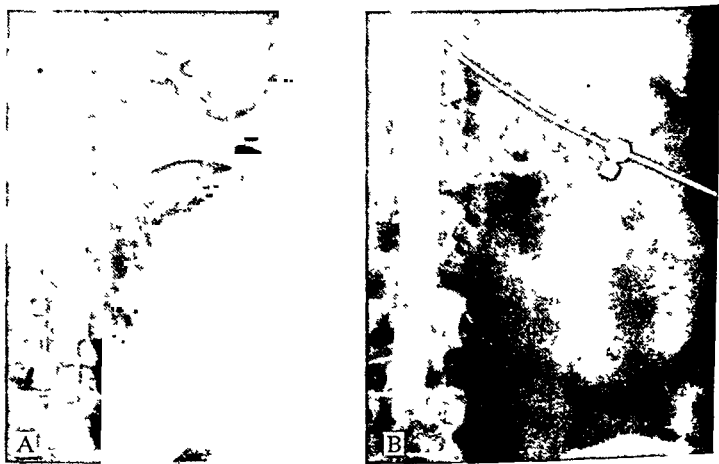


FIG. 7 A, retrograde pyelogram showing mass in lower pole left kidney, B, translumbal aortogram indicating avascularity of mass. Diagnosis renal cyst.

of the coccyx and directed medially and upward about 1-2 inches toward the concavity of the sacrum (fig. 4). Rectal palpation as the needle is advanced assists in proper placement of the needle tip in loose areolar tissue between rectum and sacrum. After the needle is appropriately placed, 3-5 cc of procaine is injected to push the rectum forward, and a three-way stopcock is attached to the

needle. Oxygen is introduced by hand injection through a 50 cc syringe attached by the stopcock and tubing to an oxygen tank. If the needle is properly placed, injection meets no appreciable resistance. The syringe is successively filled and emptied until 500–800 cc of oxygen has been injected for each side. The patient

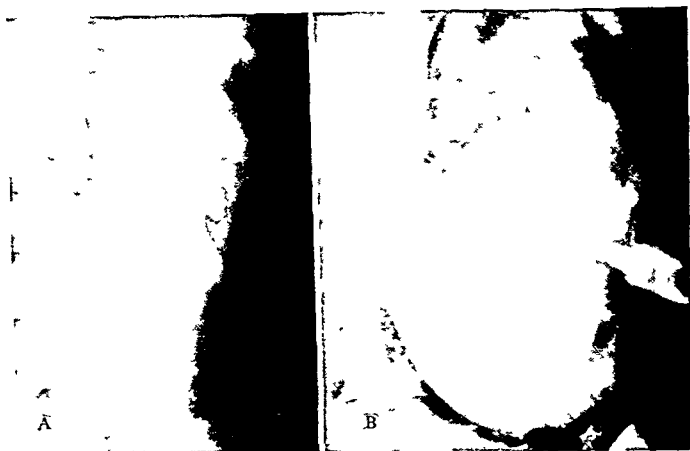


FIG. 8. *A*, left retrograde pyelogram; *B*, retroperitoneal pneumogram combined with translumbar aortogram showing lower pole mass supplied by large branch of left renal artery. Diagnosis: carcinoma of kidney, proven at surgery.



FIG. 9 Combined retroperitoneal pneumogram and translumbar aortogram. Fused ectopic kidney with anomalous blood supply. Three renal arteries well delineated.

is allowed to sit up and encouraged to move and turn to facilitate upward diffusion of the gas. A mild feeling of fullness in the flank and lumbar region indicates that oxygen has infiltrated the retroperitoneal space, and there is resonance on percussion over the lumbar area. Occasionally the patient will note shoulder (diaphragmatic) pain as the gas diffuses above the kidneys. We have not found it necessary to employ the pneumothorax apparatus recommended by others.<sup>20</sup>

In our experience manual syringe injection is efficient and safe. Oxygen has been used because it is readily available, inexpensive, and gives excellent results. It is preferred to air on the theoretical ground that a potential gas embolus with oxygen would be more readily absorbed by the blood stream.<sup>21</sup>

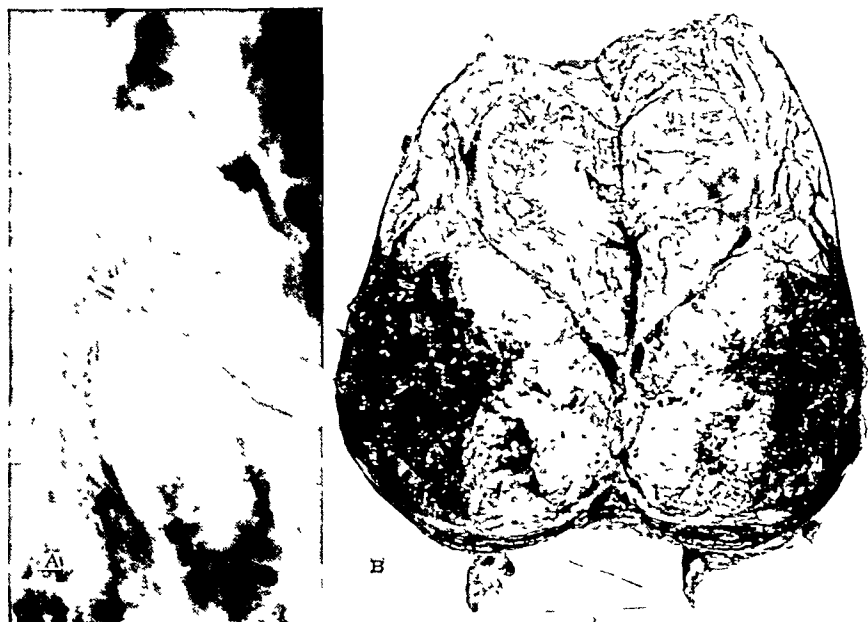


FIG. 10 *A*, misleading translumbar aortogram and retroperitoneal pneumogram: normal left renal arterial pattern with avascular contiguous mass at lower pole. *B*, surgical specimen, mixed sarcoma, extrarenal



FIG. 11. Normal retroperitoneal pneumogram and percutaneous femoral aortogram. Both adrenals can be distinguished and appear normal.

#### RESULTS

In a comparative study of translumbar and percutaneous femoral aortography, we employed both methods in each of a series of cases. In some instances the

<sup>21</sup> Goodwin, W. E. and Harmel, M. H.: *Anesth. and Analg.*, 28: 255, 1949.

patient was turned on his back immediately after the completion of aortography by translumbar aortic puncture, and percutaneous femoral artery catheterization was carried out. In others several days elapsed between utilization of each method in the same patient. In another group, only one of the two procedures was used and a comparison of results was made.



FIG. 12. White male, 10 years old, with hypertension. Retrograde pyelograms were normal. Percutaneous femoral aortography with six serial exposures at 0.5 second intervals. A, film II of series: note filling of vessels of right supra-renal mass supplied primarily by large branch from right renal artery. B, film V of series showing diffuse opacification of supra-renal mass. Diagnosis: pheochromocytoma, cured at surgery. (Courtesy of Dr. Elmer Belt.)

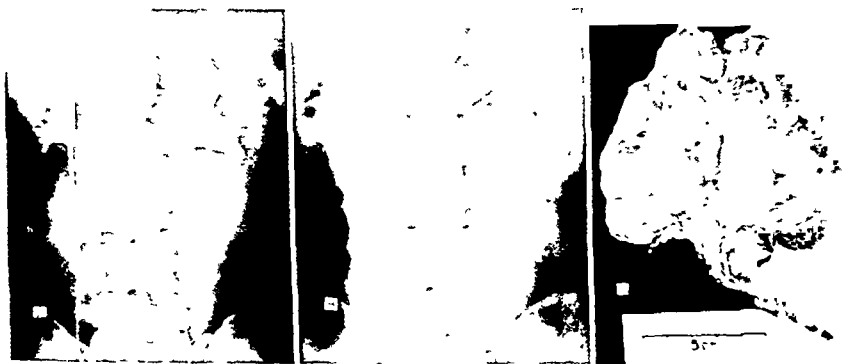


FIG. 13. White male, 34 years old, B.P. 250/170 with early cardiac failure. Poorly functioning right kidney on excretory urogram A, retrograde pyelograms. Clinical diagnosis, atrophic pyelonephritis, right. B, percutaneous femoral aortogram demonstrating normal left renal blood supply and decreased right renal vascularity. Repeated injection and translumbar aortography produced same result. C, surgical specimen. "Goldblatt kidney." Pathologist's report, obliterative renal endarteritis. At 18 month follow-up patient working and well B P 140 90.

Indications for aortography have been elaborated by many who have evaluated the technique. Vascular disease (figs. 5 and 6) is the most important non-urollogic field for aortography and arteriography. Our present study has included examples of each of the commonly listed urollogic indications for aortography. Usefulness to the urologist is apparent in cases of renal cyst (fig. 7) or tumor (fig. 8), un-

explained renal hematuria, non-functioning kidney, hydronephrosis due to aberrant vessel, renal anomalies (fig. 9), retroperitoneal tumors (figs. 10 and 12), and hypertension (fig. 13). There has been little mention of the use of aortography in evaluation of acute renal injuries. This appears to be a logical and reasonable step, and current experience of one of us suggests that it may have considerable use in this connection.

There have been no serious complications encountered with the procedures employed. On several occasions during use of the translumbar method, extravasation of contrast medium about the aorta occurred. The result was deep abdominal discomfort which disappeared within 24 hours.

The site of percutaneous femoral artery puncture is usually tender to pressure for one or two days. Some ecchymosis is present for about one week. Use of pressure dressing over the puncture site after removal of the tubing has prevented bleeding and hematoma formation.

No ill effects were noted after retroperitoneal oxygen insufflation.

#### CONCLUSIONS

Both translumbar and percutaneous femoral methods of aortography are useful. There are specific indications for the use of each method (table 1).

TABLE 1

|                              | <i>Indications</i>                                                                                                                                                                                                                                                                          | <i>Contraindications</i>                                                                                                                                                                |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Translumbar method:          | Most cases of simple, renal arteriography (fig. 7)<br>Peripheral vascular disease or obliterative disease of the aorta (fig. 6)                                                                                                                                                             | Lumbar aortic aneurysm (fig. 5)<br>Some cases of scoliosis where lumbar method is difficult or impossible<br>Inflammatory disease of lumbar spine, left lumbar or retroperitoneal areas |
| Percutaneous femoral method: | Visualization of adrenals (figs. 11 and 12)<br>Aortic aneurysm (fig. 5)<br>Desire to fill aorta above diaphragm (fig. 11)<br>Most children (fig. 12)<br>Where movement of patient (i.e. for oblique x-rays, etc.) is desired<br>Casts or orthopedic appliances which prevent prone position | Peripheral vascular disease<br>Very obese patients<br>Local lesions of inguinal region; hernia, lymphadenopathy, inflammatory disease                                                   |

The novice may learn both methods with relative ease. In our experience the translumbar method is quicker and easier and usually gives better roentgenographic results. The femoral puncture method has the distinct advantage of mobility of the tubing and thus the site of injection of contrast medium.

Either method can be safely and easily used with local infiltration anesthesia only.

A test injection of contrast medium with a "scout" x-ray film is important as a preliminary step in each method. It provides additional protection for the patient and helps assure optimal results.

Either 75 per cent neo-iopax or 70 per cent urokon as a contrast medium is well tolerated by the patient and gives arteriograms of good quality.

The use of serial x-ray exposures is of definite aid and should be employed whenever possible in aortography by either technique.

Retroperitoneal oxygen injection by way of the presacral route is simple and harmless. Often the resulting x-rays give a remarkable amount of information in themselves. When combined with aortography, by either route, the diagnostic value of each technique is enhanced (fig. 9). This combination should often be used in difficult problems.

#### SUMMARY

A comparative study of translumbar aortic puncture and percutaneous femoral artery catheterization methods of aortography has been made.

The basic techniques of each method are described, and modifications of equipment and procedure are presented in detail.

The use of local infiltration anesthesia, a special needle for aortography, and the needle stop with the translumbar method is described.

The importance of a test injection of contrast medium employed with a "scout" x-ray film as a preliminary step with either method is emphasized.

The selection and use of contrast media are discussed.

Advantages of serial x-ray films, obtained with the rapid cassette-changing device (Sanchez-Perez seriograph), using either technique of aortography are enumerated.

The use of retroperitoneal pneumography with aortography for greater diagnostic detail is reported, and the technique of pre-sacral oxygen injection is described.

Results obtained with translumbar and percutaneous femoral aortography alone and in combination with retroperitoneal pneumography are illustrated.

Grateful acknowledgement is made to our medical illustrator, Mary P. Goodwin, and the members of the photographic laboratory, Wadsworth Hospital.

*1015 Gayley Ave. Los Angeles 24, Calif. (R. C. W.)*

*The Department of Surgery, Division of Urology, The University of California, Los Angeles 24, Calif. (W. E. G.)*



## REACTION TO UROGRAPHIC AGENTS WITH AND WITHOUT ANTIHISTAMINES

THOMAS D. MOORE AND NELSON SANDERS

*From the University of Tennessee, The Department of Urology, John Gaston Hospital and Moore Clinic, Memphis, Tenn.*

Almost a quarter century has elapsed since von Lichtenberg and Swick<sup>1</sup> demonstrated the clinical value of the organic iodine compounds in the diagnosis of lesions of the urinary tract. During this period excretion urography has become one of the most commonly used and a most valuable diagnostic tool in the hands of the urologist. No reliable figure on the number of excretory urograms made in this country is available, but the number must be well in excess of a million yearly.

Although the use of modern urographic agents is generally considered safe, the reports of serious reactions and even fatalities following excretion urography command attention. Any means by which the risk of excretory urography, a wholly diagnostic procedure, can be eliminated or reduced takes on an importance greater perhaps than the relative infrequency of serious accidents would seem to indicate. Careful observations on reactions to urographic agents have been made for the past several years at the Moore Clinic and the John Gaston Hospital in Memphis. Because our approach to the problem has contained some features not emphasized in other reports, we believe that we are justified in presenting our preliminary findings, although inconclusive, in the hope that further work along these or similar lines will be stimulated.

Reactions to urographic media are usually classified as "mild," "moderate," "severe," or "fatal," for they appear to be qualitatively similar differing one from another only in their severity. They consist of flushing of the skin, particularly of the upper half of the body, nausea and vomiting, sneezing, itching and urticaria. The more severe reactions may be characterized by edema of the eyelids, lacrimation, laryngospasm, bronchospasm, vertigo, pallor of the skin, syncope, cyanosis and the other evidences of shock. Symptoms appear early either during or shortly after completion of the injection. The nature of the reactions themselves, their relative infrequency, their tendency to occur in patients with an allergic history and the fact that the amount of contrast medium injected seems unimportant all suggest that these reactions are allergic or anaphylactoid in nature. Nausea and vomiting may, however, represent an exception, conceivably resulting from direct stimulation of the vomiting center by the contrast medium.

One widely used urographic agent, Diodrast, can be injected intravenously in doses of 100 cc of a 70 per cent solution for angiocardiology as a rule without the production of serious side effects, whereas a fatal reaction has been ascribed to one two-hundredth of this dose. Such considerations as these lead us to believe that the intrinsic toxicity of the drug is not responsible for reactions. Inasmuch

Accepted for publication October 13, 1952.

<sup>1</sup> von Lichtenberg and Swick: *Klin. Wchnschr.*, No. 45, p. 2089, 1929.

in the production of tics which is not generally conceded it may be important that in the treatment of sensitive patients in general, the use of anticholinergic agents for the prevention of further contractions in unresponsive limbs has been that of a limited investigation. For the results of previous studies are not known.

Several investigators (5, 11, 12) use Pyridostigmine (2-hydroxy-2-dimethyl-5,6-methylenedioxy-3-methylpyridine) HCl orally 1 hour before recombined myography. In a series of 17 patients, patients with negative clonus histories and negative recombined and standardized sensitivity tests in 12 cases. In subsequent experiments of Duchen it was observed in patients receiving atropine. Several reports of this use as a means of reducing or even preventing any contractions with anticholinergic drugs is not a new one. In a group of 2 patients all with clonus, atropine was administered in solution in Duchen on one or both of the tests immediately preceding them with only four patients after treatment with oral Pyridostigmine.

In a later report of a larger group of 200 patients, Duchen confirms his previous findings that anticholinergic drug Pyridostigmine reduced the incidence of contractions in Duchen.

Dusen found that both the number and severity of Duchen contractions were reduced in patients pretreated by the intramuscular or subcutaneous injection of the anticholinergic drug benactyl (2-(2-hydroxyethyl)-1-methyl-4-piperidine HCl) which compared with a 100 percent of patients not so pretreated. After demonstrating to patients first that the anticholinergic substance Benactyl (2-hydroxyethyl)-1-methyl-4-piperidine HCl retained its activity when mixed with Duchen's. Dusen found that the incidence of contractions could be even further reduced when the Benactyl was incorporated with the Duchen solution and both substances oriented intravenously together. The preparation which Dusen used contained 20 mg of Benactyl in 20 cc of 0.9 per cent Duchen. It is interestingly that the same dose of Duchen's, apparently used by Dusen, is 20 cc of 0.9 per cent solution whereas most analogists use 20 cc Dusen further points out that regardless of the amount of Duchen used, the dose of Benactyl should not exceed 20 mg.

In a later communication Dusen reports the results of studies on a larger series of cases of 100 patients in whom Duchen was injected without an anticholinergic 20 per cent showed contractions. In 80 patients who received Duchen in which Benactyl had been incorporated, only 4 per cent experienced any reaction. Side effects when they occurred in this latter group were mild.

Dusen et al. (13) also report on the value of anticholinergic premedication not only in the clinical nature of such contractions. These investigators in a very carefully controlled study administered Duchen for extensor myography to two groups of closely observed patients. Each group was composed of about

5. Dusen, J. L. *New England Med. & Surg. J.* 1941; 185: 123.  
 11. Dusen, J. L. *J. Pediatr.* 55: 116, 1958.  
 12. Dusen, J. L. *Ann. Entomol. Soc. Am.* 55: 116, 1962.  
 13. Dusen, J. L., Dusen, J. L. and DeLeonardis, R. *Ann. New York Acad. Sci.* 1964.

## REACTION TO UROGRAPHIC AGENTS WITH AND WITHOUT ANTIHISTAMINES

THOMAS D. MOORE AND NELSON SANDERS

*From the University of Tennessee, The Department of Urology, John Gaston Hospital and Moore Clinic, Memphis, Tenn.*

Almost a quarter century has elapsed since von Lichtenberg and Swick<sup>1</sup> demonstrated the clinical value of the organic iodine compounds in the diagnosis of lesions of the urinary tract. During this period excretion urography has become one of the most commonly used and a most valuable diagnostic tool in the hands of the urologist. No reliable figure on the number of excretory urograms made in this country is available, but the number must be well in excess of a million yearly.

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One widely used urographic agent, Diodrast, can be injected intravenously in doses of 100 cc of a 70 per cent solution for angiocardiology as a rule without the production of serious side effects, whereas a fatal reaction has been ascribed to one two-hundredth of this dose. Such considerations as these lead us to believe that the intrinsic toxicity of the drug is not responsible for reactions. Inasmuch

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production of reactions, two new salts were studied. Commercial Diodrast is the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid. The fourth solution consisted of a 35 per cent solution of the methyl glucamine salt of 3,5-diiodo-4-pyridone-N-acetic acid. This preparation has been used for cerebral-angiography and is said to be less irritating and to pass less readily through the blood-brain barrier than the diethanolamine salt. The fifth solution (the sodium salt of 1-(3,5-diiodo-4-pyridone)-propanoate was studied only on private white patients, and its identity was known to the observer.

All solutions were used in exactly the same manner and in accordance with our usual urographic technique; i.e., 1 cc was injected intravenously and then without removing the needle from the vein several minutes were allowed to elapse to see whether any reaction occurs. In neither series was any untoward

TABLE 1. Series 1, charity patients

| SOLUTION                    | NO. PATIENTS | REACTIONS (PER CENT) |          |          |          |                        |                       |            | PATIENTS SHOWING NO REACTIONS (PER CENT) |
|-----------------------------|--------------|----------------------|----------|----------|----------|------------------------|-----------------------|------------|------------------------------------------|
|                             |              | Nausea               | Vomiting | Sweating | Flushing | Urticaria and Pruritus | Respiratory* Symptoms | Vein Cramp |                                          |
| Diethanolamine salt†.....   | 58           | 24.1                 | 5.2      | 1.7      | 19.0     | 6.9                    | 10.3                  | 3.4        | 51.9                                     |
| Methyl glucamine salt‡..... | 50           | 30.0                 | 6.0      | 10.0     | 14.0     | 4.0                    | 4.0                   | —          | 50.0                                     |
| Diodrast w/Benadryl.....    | 56           | 25.0                 | 3.6      | 7.1      | 23.2     | 3.6                    | 5.4                   | —          | 55.4                                     |
| Diodrast w/ThenfadiI.....   | 58           | 15.5                 | —        | 3.4      | 19.0     | —                      | 1.7                   | —          | 60.5                                     |

Note: Some patients experienced more than one reaction.

\* Choking sensation, transient dyspnea and sneezing.

† Diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid.

‡ Methyl glucamine salt of 3,5-diiodo-4-pyridone-N-acetic acid.

reaction produced by the test dose so that all these patients may be considered "non sensitive" within the limitations of this test. The remainder of the solution was then injected slowly at a rate of 5 or 6 cc per minute.

The number and nature of the reactions observed in the case of series 1 are shown in table 1.

#### COMMENT

Comparing the 2 salts of 3,5-diiodo-4-pyridone-N-acetic acid, the methyl glucamine salt appeared to cause somewhat more sweating and somewhat fewer respiratory symptoms than the diethanolamine salt, although the differences were not striking.

Of the two antihistamines the preparation containing ThenfadiI seemed to cause fewer reactions in all categories than that containing Benadryl. The solutions containing antihistamines seemed to produce fewer reactions than the solutions not containing antihistamines.

Blood pressure readings were made before and after injection on all patients in both series. The fluctuations in general were minimal and about as many rises were recorded as falls. In two instances both in Series I, one after injection of

100 subjects. One group received no antihistamine premedication, the second was premedicated with Pyribenzamine orally and the third with Trimeton [1-phenyl-1-(2-pyridyl)-3-dimethylaminopropane] orally. The unpremedicated patients actually exhibited fewer reactions than those in either of the premedicated groups. They concluded that antihistamine premedication did not influence the incidence, severity or type of reactions to Diodrast. They did observe, however, that patients giving a history of allergy, particularly asthma, were more apt to experience reactions than those without such a history. In this series of patients receiving Trimeton, shock developed in one; in three others syncope. Although it is not stated how much Diodrast was injected, it is assumed that the amount was 30 cc of 35 per cent solution.

The present study was designed to try to eliminate as much as possible extraneous factors which might complicate interpretation of the results. Realizing that race, social status and educational level frequently influence subjective reactions to drugs the study was divided into two parts. Series 1 was comprised of charity patients, nearly all of whom belonged to the Negro race. Their nutritional state and their social and educational level were lower than the patients composing series 2, who were all white private patients. Patients of lower educational level such as those comprising series 1 are certainly more susceptible to suggestion and respond more readily to minor influences stemming from the physician's attitude. As a rule, they have greater fear and less understanding of what is being done for them. Their interpretation of subjective phenomena might be expected to differ from patients with a higher educational and cultural background.

The discrepancy in results so often reported by observers and the frequency with which one finds such statements in published literature as "in our hands" or "in our hospital" bear eloquent testimony to the fact that a critical study of this complex problem is inordinately difficult. We have endeavored to avoid the "in my hands" pitfall by having the observations on the two series of cases made by different investigators working independently and by use of the so called "blind study" method.

Four of the solutions studied were labeled only A, B, C and D so that neither observer had any knowledge of their identity. Each solution was administered to patients in rotation so that the number of patients in each series receiving each solution was roughly equal. In order to check any qualitative difference that might exist between antihistamine agents, two such drugs were used. One solution consisted of regular commercial Diodrast 35 per cent, to each 30 cc vial of which had been added 20 mg. of Benadryl. The second solution contained 30 cc of Diodrast 35 per cent, to which 6 mg. of the antihistamine Thenfadil had been added (6 mg. of Thenfadil is pharmacologically about the equivalent of 20 mg. of Benadryl). The third solution was 35 per cent Diodrast used as a control. It was of the same manufactured lot as that used in preparing the Diodrast antihistamine solutions.

In an effort to determine whether the salt of Diodrast played a part in the

to antihistamine preparations. Nevertheless, undue drowsiness, although infrequent, was recorded wherever found. In both series it occurred three times after the injection of Diodrast with Benadryl, six times after injection of Diodrast with Thenfadil and one time after the injection of the diethanolamine salt.

All of the solutions gave excellent urograms of approximately equal density.

TABLE 3. Series 1 and 2 Combined

| SOLUTION                 | NO. PATIENTS | REACTIONS (PER CENT) |          |          |        |          |                        |                       |            |       | PATIENTS SHOWING NO REACTIONS (PER CENT) |
|--------------------------|--------------|----------------------|----------|----------|--------|----------|------------------------|-----------------------|------------|-------|------------------------------------------|
|                          |              | Nausea               | Vomiting | Sweating | Pallor | Flushing | Urticaria and Pruritus | Respiratory* Symptoms | Vein Cramp | Shock |                                          |
| Diethanolamine salt†.... | 111          | 23.4                 | 5.4      | 9.9      | 2.7    | 19.8     | 9.9                    | 6.3                   | 3.4        | —     | 55.0                                     |
| Sodium salt‡.....        | 69           | 8.6                  | 4.3      | 8.7      | 2.9    | —        | —                      | —                     | 13.0       | 1.5   | 75.4                                     |
| Methyl glucamine salt§.. | 101          | 16.4                 | 3.8      | 10.6     | 1.9    | 9.6      | 3.8                    | 4.8                   | —          | —     | 66.2                                     |
| Diodrast w/Benadryl....  | 110          | 16.3                 | 1.8      | 10.9     | 3.6    | 14.5     | 3.6                    | 2.7                   | —          | —     | 64.3                                     |
| Diodrast w/Thenfadil...  | 116          | 12.1                 | —        | 8.6      | 4.3    | 12.1     | 0.9                    | 0.9                   | —          | —     | 68.1                                     |

Note: Some patients experienced more than one reaction.

\* Choking sensation, transient dyspnea and sneezing.

† Diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid.

‡ Sodium salt of 1-(3,5-diiodo-4-pyridone)-propanoate.

§ Methyl glucamine salt of 3,5-diiodo-4-pyridone-N-acetic acid.

TABLE 4. Series 1 and 2, patients giving history of allergy

| SOLUTION                  | NO. PATIENTS | REACTIONS (PER CENT) |          |          |        |          |                        | PATIENTS SHOWING NO REACTIONS (PER CENT) |
|---------------------------|--------------|----------------------|----------|----------|--------|----------|------------------------|------------------------------------------|
|                           |              | Nausea               | Vomiting | Sweating | Pallor | Flushing | Urticaria and Pruritus |                                          |
| Diethanolamine salt*..... | 7            | 42.8                 | 14.3     | 28.6     | 14.3   | 28.6     | 14.3                   | 42.8                                     |
| Sodium salt‡.....         | 4            | 75.0                 | 25.0     | —        | —      | —        | —                      | 50.0                                     |
| Methyl glucamine salt‡... | 7            | 28.6                 | 28.6     | 14.3     | —      | 28.6     | —                      | 57.1                                     |
| Diodrast w/Benadryl.....  | 8            | 12.5                 | —        | —        | —      | 37.5     | —                      | 62.4                                     |
| Diodrast w/Thenfadil..... | 6            | 33.3                 | —        | —        | —      | —        | —                      | 66.7                                     |

Note: Some patients experienced more than one reaction.

\* Diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid.

‡ Sodium salt of 1-(3,5-diiodo-4-pyridone)-propanoate.

‡ Methyl glucamine salt of 3,5-diiodo-4-pyridone-N-acetic acid.

The number of patients in both series giving a history of allergy was small; however, as expected they showed a greater percentage of side effects. The results are shown in table 4.

## SUMMARY

Four solutions, one containing Diodrast (diethanolamine salt); a second containing the methyl glucamine salt of 3,5-diiodo-4-pyridone-N-acetic acid; a third containing a mixture of Diodrast with Benadryl; and a fourth containing Diodrast and Thenfadil were compared on two widely differing types of patients by two observers acting independently in a "blind study." A fifth solution con-

Diodrast with Thenfadil and the other after injection of the methyl glucamine salt, there was a moderate fall which was considered to be due to other circumstances than the injection.

The results following the injection of the same four solutions and a fifth in series 2 are shown in table 2.

In these patients, with the exception of respiratory symptoms, there seemed to be a fairly consistent reduction in side effects following the injection of the methyl glucamine salt and the sodium salt when compared with the injection of the diethanolamine salt, but there was one severe reaction with the sodium salt. The patient lost consciousness, stopped breathing and the blood pressure was unobtainable. Resuscitative measures were, however, successful, and there was no permanent ill effect. The sodium salt was more prone to produce vein

TABLE 2. *Series 2, private patients*

| SOLUTION                 | NO. PATIENTS | REACTIONS (PER CENT) |          |          |        |          |                        |                      |            |       | PATIENTS SHOWING NO REACTIONS (PER CENT) |
|--------------------------|--------------|----------------------|----------|----------|--------|----------|------------------------|----------------------|------------|-------|------------------------------------------|
|                          |              | Nausea               | Vomiting | Sweating | Pallor | Flushing | Urticaria and Pruritus | Respiratory Symptoms | Vein Cramp | Shock |                                          |
| Diethanolamine salt†.... | 53           | 22.6                 | 5.7      | 18.9     | 5.7    | 20.7     | 13.2                   | 1.9                  | —          | —     | 58.5                                     |
| Sodium salt‡.....        | 69           | 8.6                  | 4.3      | 8.7      | 2.9    | —        | —                      | —                    | 13.0       | 1.5   | 75.4                                     |
| Methyl glucamine salt§.. | 54           | 3.7                  | 1.9      | 11.0     | 3.7    | 5.5      | 3.7                    | 5.5                  | —          | —     | 81.4                                     |
| Diodrast w/Benadryl....  | 54           | 7.4                  | —        | 14.8     | 7.4    | 5.6      | 3.7                    | —                    | —          | —     | 74.0                                     |
| Diodrast w/Thenfadil...  | 58           | 8.6                  | —        | 13.8     | 8.6    | 5.2      | 1.7                    | —                    | —          | —     | 76.0                                     |

Note: Some patients experienced more than one reaction.

\* Choking sensation, transient dyspnea and sneezing.

† Diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid.

‡ Sodium salt of 1-(3,5-diiodo-4-pyridone)-propanoate.

§ Methyl glucamine salt of 3,5-diiodo-4-pyridone-N-acetic acid.

cramp than any of the other solutions. Solutions containing both antihistamine drugs seemed to be better tolerated than that consisting of the diethanolamine salt although there was no difference between the two antihistamines.

The only instance of fainting in either series occurred here after the injection of Diodrast containing Thenfadil. It occurred about two hours after the injection under circumstances which made it probable that the reaction was unrelated to the injection.

Table 3 represents a combination of data contained in tables 1 and 2.

#### COMMENT

When all types of patients and the observation of two different observers are combined the differences between the various solutions are even less striking. The methyl glucamine salt seems to be somewhat better tolerated in general than the diethanolamine salt. With the exception of pallor and flushing, Diodrast with Thenfadil appears to be superior to the other solutions. In general, Diodrast with antihistamine seems to cause fewer reactions than commercial Diodrast.

The purpose of this experiment was to evaluate reactions to Diodrast and not

## URIC ACID CALCULI: WITH PARTICULAR REFERENCE TO DETERMINATIONS OF URIC ACID CONTENT OF BLOOD\*

WILBUR A. ARMSTRONG AND LAURENCE F. GREENE

*From the Mayo Foundation, University of Minnesota and Section of Urology, Mayo Clinic, Rochester, Minn.*

Urologists are frequently confronted by patients complaining of recurrent attacks of renal colic who may or may not have passed urinary calculi. In some instances urologic investigation yields negative results: excretory urography, retrograde pyelography and cystoscopy fail to disclose the cause of their symptoms. In spite of lack of evidence the urologist may be of the opinion that the patient's symptoms result from urinary calculi. He is aware that approximately 10 per cent of urinary calculi are nonopaque roentgenographically and that demonstration of small nonopaque urinary calculi may be extremely difficult. Furthermore, he is aware that the majority of such calculi are composed of uric acid. What steps can be taken, therefore, to exclude uric acid calculi as cause for the patient's symptoms?

Obviously, if the patient has passed and recovered a calculus, the diagnosis may be established by analysis of the stone. If a stone is not available, a description of the stones passed previously may be helpful. Uric acid stones are usually golden brown or yellow. If the patient does not have a history of passage of calculi, microscopic examination of urinary sediment for uric acid crystals may be of aid. Finally a diagnosis of gout may be helpful inasmuch as approximately 13 per cent of patients with this disease are afflicted also with uric acid calculi.<sup>1</sup>

To our knowledge the value of determinations of the uric acid content of the blood of patients suspected of having uric acid calculi has not been established. In other words, if the presence of uric acid calculi is suspected, how much help in diagnosis is afforded by determination of the uric acid content of the blood?

In an attempt to answer this question we reviewed the records of all patients at the Mayo Clinic who were found to have uric acid calculi and for whom determination of the uric acid content of the blood had been made during the years 1939 to 1950 inclusive.\*

Accepted for publication July 30, 1952.

Chemical analyses of the calculi and determinations of the uric acid content were performed under the direction of Dr. M. H. Power, Section of Biochemistry, Mayo Clinic.

\* Classification of calculi was made by abridged application of the scheme of Hawk and Bergeim, in which qualitative detection of uric acid is made by means of the murexide reaction. (Hawk, P. B. and Bergeim, Olaf: *Practical Physiological Chemistry*. Ed. 11, Philadelphia: P. Blakiston's Son and Co., Inc., 1937, 96S pp.) Determinations of the uric acid content of the blood or serum were made by the method of Folin (J. Biol. Chem. 54: 153-170, 1922) except that protein-free filtrates were prepared by the use of combined solutions of sodium tungstate and sulfuric acid rather than the separate solutions of Folin. Prior to 1946, whole blood was employed in this test and normal values were considered to be 2 to 4 mg. per 100 cc of blood. Subsequent to that time serum has been employed and the normal values are 4 to 6 mg. per 100 cc of serum. Values for uric acid greater than 6 mg. were considered to be elevated.

<sup>1</sup> Hench, P. S., Bauer, Walter, Boland, E. W., Crain, D. C., Freyberg, R. H., Graham, Wallace, Holbrook, W. P., Lockie, L. M., McEwen, Currier, Rosenberg, E. F. and Stecher, R. M.: Rheumatism and arthritis. Review of American and English literature of recent years (ninth rheumatism review). *Ann. Int. Med.*, 28: 66-16S, 1948.



taining the sodium salt of 1-(3,5-diiodo-4-pyridone)-propanoate was studied in one type of patient only. In all, the investigation included observations on a total of 510 patients. The methyl glucamine salt appeared to be somewhat better tolerated than the diethanolamine salt. The use of a potent antihistamine with Diodrast appeared to offer some advantage from the standpoint of reduction of side effects. No severe or alarming reactions were encountered, except with the use of the sodium salt of (1-3,5-diiodo-4-pyridone)-propanoate.

Since both a change of the salt of Diodrast and addition of an antihistamine to Diodrast 35 per cent solution appeared to decrease the incidence of reactions the next step seems clear. A combination of the methyl glucamine salt of 3,5-diiodo-4-pyridone-N-acetic acid and some potent antihistamine such as Thenfadil should be studied.

We are indebted to Winthrop-Stearns, Inc., New York, for furnishing the material for this study. We should also like to express our gratitude to Dr. J. B. Rice, Director of the Medical Research Department, for his kind assistance.

*899 Madison Ave., Memphis 3, Tenn.*

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Obviously, if the patient has passed and recovered a calculus, the diagnosis may be established by analysis of the stone. If a stone is not available, a description of the stones passed previously may be helpful. Uric acid stones are usually golden brown or yellow. If the patient does not have a history of passage of calculi, microscopic examination of urinary sediment for uric acid crystals may be of aid. Finally a diagnosis of gout may be helpful inasmuch as approximately 13 per cent of patients with this disease are afflicted also with uric acid calculi.<sup>1</sup>

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Our series is composed of 117 patients who had uric acid calculi and who had had determinations of the serum uric acid at the same admission. Men predominated in this group with the highest incidence in the sixth decade of life. Calculi were removed from various parts of the urinary tracts of 60 patients by surgical measures. The calculi were situated in the kidney in 29 cases, in the ureter in 16 cases and in the bladder in 15 cases. In a significant number of the operative procedures the exact diagnosis was not made until the time of surgical exploration. Thus, for example, a preoperative diagnosis of ureteral obstruction of indeterminate nature was made and only surgical exploration determined that the obstruction was due to uric acid calculi. In 57 cases the stones were sufficiently small in size to pass spontaneously; many of these patients had passed numerous stones previously.

Roentgenographic studies revealed the calculi to be nonopaque in 60 per cent of the cases. In 13 per cent of the cases the calculi were faintly opaque; these calculi could be identified in retrospect in roentgenograms when their locations

TABLE 1. *Uric acid content of blood of patients with uric acid calculi*

|                   | CASES | URIC ACID CONTENT ABOVE NORMAL |          |
|-------------------|-------|--------------------------------|----------|
|                   |       | Number                         | Per cent |
| Without gout..... | 85    | 18                             | 21       |
| With gout*.....   | 32    | 25                             | 78       |
| Total.....        | 117   | 43                             | 37       |

\* In addition, 3 patients had leukemia and 2 had polycythemia vera.

were known. In the remaining 27 per cent of the cases the calculi were opaque and were readily seen in the roentgenograms. Inasmuch as pure uric acid calculi are nonopaque, the calculi in the latter groups consisted of mixtures of uric acid and other substances.

The aspect of the problem of particular interest to us was the uric acid content of the blood in these patients. Of the 117 patients with uric acid calculi, 32 were also afflicted with gout; in addition, among the 32 patients were 3 suffering from leukemia and 2 from polycythemia vera. The findings in respect to the uric acid values are shown in table 1. It will be noted that only 21 per cent of patients with uric acid calculi who did not have gout had hyperuricemia. On the other hand 78 per cent of patients with uric acid calculi who were also afflicted with gout had hyperuricemia. Considering the group as a whole, irrespective of the presence or absence of gout or other diseases commonly associated with elevation of the uric acid content of the blood, only 37 per cent of patients with uric acid calculi had hyperuricemia. The hyperuricemia was not a manifestation of azotemia inasmuch as the content of urea in the blood was higher than normal for only 4 of these patients.

#### SUMMARY

The purpose of this study was to investigate the diagnostic values of determinations of the uric acid content of the blood in patients who are suspected of

having uric acid calculi. It was found that the majority of patients with uric acid calculi did not have hyperuricemia. A majority of patients who, in addition to having uric acid calculi, had symptoms compatible with gout exhibited hyperuricemia. The patients afflicted with gout, however, usually do not present a diagnostic problem. In other words, if a patient with gout experiences attacks of renal colic the likelihood that these attacks are produced by uric acid calculi is great. The patient who presents a problem to the urologist is one who complains of renal colic suggestive of urinary calculi, who does not have gout and in whom urinary calculi cannot be demonstrated by usual urologic procedures. Hyperuricemia can be expected in only 21 per cent of patients of this type.

Thus, our study reveals that the majority of patients who have uric acid calculi do not have hyperuricemia. The uric acid content of the serum should be determined for patients suspected of suffering from calculous disease which cannot be demonstrated roentgenographically. Hyperuricemia and gout may be considered as suggestive evidences of the presence of uric acid calculi. Normal values do not exclude uric acid calculi inasmuch as the values for serum uric acid were normal in two thirds of the group of patients with uric acid calculi.

## EFFECT OF RENAL FUNCTION ON EXCRETION OF SULFADIMETINE GIVEN IN SMALL DOSES FOR URINARY INFECTION

RICHARD W. LIPPMAN\* AND HELEN U. MARTI

*From the Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, Calif.*

The use of minimal doses of sulfonamide (sulfathiazole) to treat chronic urinary infection was first suggested by Helmholz,<sup>1</sup> who found, in a patient with impaired renal function due to chronic pyelonephritis, that a sensitivity reaction to the sulfonamide could be avoided while bacteruria and pyuria were prevented with a dose as low as 0.125 g. twice a day. Helmholz also studied the concentration of sulfathiazole necessary to produce a bactericidal effect in vitro.<sup>2-5</sup> He found some variation in the effectiveness of sulfanilamide, sulfathiazole, and sulfamethylthiazole against organisms isolated from the urine. Sulfathiazole appeared to be the most effective bactericidal agent of these, with a wide range of effectiveness at 30 mg. per cent and with a slightly diminished but still considerable range at 10 mg. per cent.

Addis<sup>6</sup> adopted the low dose-sulfathiazole regime in the management of chronic pyelonephritis, and had considerable success. Although Addis mentions 2 patients who manifested sensitivity reaction, even with a dose of 0.100 g. four times a day,<sup>†</sup> other patients who had been sensitive to the usual large dose were able to tolerate the small dose without toxic effects. Addis maintained patients on the regimen as long as seven years, without sensitivity reactions unless they had developed within the first month and with success in preventing bacteruria and pyuria.

We have followed a routine similar to that of Helmholz and Addis in the management of patients with chronic pyelonephritis. Bacteruria, pyuria, and recurrences of acute pyelonephritis have been eliminated by the medication in most cases. Some of our patients have taken the sulfonamide steadily for as long as four years. We usually begin treatment with a short course of terramycin or chloramphenicol in full dosage, followed by one of several sulfonamides (sulfathiazole, sulfamerazine, sulfadimetine) in a dose of 0.125 g. four times a day. Only in unusual instances has a patient had to discontinue the medication because of a rash or nausea within the first month of administration. No toxic signs or symptoms have been observed after the first month and no major toxic reactions have occurred.

This work was supported by a grant from Ciba Pharmaceutical Products, Inc., Summit, N. J.

\* Fellow of the John Simon Guggenheim Memorial Foundation.

† Marshall, McNamara, and Schulte<sup>7</sup> have reported a case of fatal agranulocytosis after 40 days of sulfadiazine administration, 0.500 g. daily.

<sup>1</sup> Helmholz, H. F.: Proc. Staff Meet., Mayo Clin., 16: 145, 1941.

<sup>2</sup> Id., *ibid.*, 15: 65, 1940.

<sup>3</sup> Id., *ibid.*, 16: 149, 1941.

<sup>4</sup> Id., *ibid.*, 17: 202, 1942.

<sup>5</sup> Id., J. Urol., 46: 322, 1941.

<sup>6</sup> Addis, T.: Glomerular Nephritis. New York: Macmillan, 1948, p. 176.

<sup>7</sup> Marshall, M., Jr., McNamara, T. M. and Schulte, J. W.: Calif. Med., 72: 390, 1950.

Although most have had a successful therapeutic response, occasional patients have not responded until the dose of sulfonamide was doubled or tripled. Rare patients have not shown any favorable therapeutic effect, with continuing bacteruria and pyuria. Because of these clinical observations, and because we had noticed that the therapeutic difficulties were most frequent in patients with impaired renal function, we wondered whether the occasional therapeutic failures were due to resistant bacteria or to altered excretion of the drug. This experiment was undertaken to learn whether impaired renal function significantly altered the urinary sulfonamide concentration attained on a fixed dosage schedule.

#### METHODS

Human subjects were given 0.125 g. tablets of sulfadimetine\* and were instructed to take one tablet on arising, one before lunch, one before supper, and one before retiring, a total of four each day. Each subject was instructed to be faithful in taking the medication and in reporting omissions, and the purpose of the experiment was explained. Set times for each dose were deliberately avoided, since it was deemed preferable to obtain information concerning the urinary sulfonamide concentration under conditions of ordinary, protracted clinical use. After one week of sulfadimetine administration, urine collections were made at the following intervals: 7 a.m. to 12 noon, 12 noon to 5 p.m., 5 p.m. to 10 p.m., and 10 p.m. to 7 a.m. Venous blood was drawn in the following morning.

Creatinine determinations were performed on serum and on the urine specimen collected from 10 p.m. to 7 a.m., by the method of Bonsnes and Taussky.<sup>8</sup> As was first indicated by Oosterheld,<sup>9</sup> the conventional method of Bratton and Marshall<sup>10</sup> for the determination of sulfonamide content in blood and urine is not satisfactory for certain sulfonamides, including sulfadimetine. For the determination of free sulfadimetine in the urine and urine specimens, therefore, we used a slight modification of the method of Druey and Oosterheld,<sup>11</sup> which gave excellent recoveries of standard amounts. The determination of acetylsulfadimetine was not entirely satisfactory in our hands. If the conditions of hydrolysis were made sufficiently drastic to obtain complete hydrolysis, some decomposition occurred. Recovery of standard could not be obtained with satisfactory consistency. For these reasons the apparent gross change in acetylation, observed in uremic individuals, is reported in qualitative terms only.

The subjects were divided into two groups. In one group ("normal") were 9 individuals in whom 12 series of determinations were performed. In this group, since there were no significant differences among them, normal individuals were included as well as individuals with renal disease but with a serum creatinine concentration less than 2.00 mg. per cent and an endogenous creatinine clearance within normal limits. In the second group ("azotemic") were 6 individuals with chronic pyelonephritis and azotemia, with serum creatinine concentrations that

\* Elkosin<sup>®</sup>, supplied by Ciba Pharmaceutical Products, Inc.

<sup>8</sup> Bonsnes, R. W. and Taussky, H. H.: *J. Biol. Chem.*, 158: 581, 1945.

<sup>9</sup> Oosterheld, G.: *Schweiz. med. Woch.*, 70: 459, 1940.

<sup>10</sup> Bratton, A. C. and Marshall, E. K., Jr.: *J. Biol. Chem.*, 128: 537, 1939.

<sup>11</sup> Druey, J. and Oosterheld, G.: *Helv. Chim. Acta*, 25: 753, 1942.

varied from 2.49 mg. per cent to 11.81 mg. per cent and with marked diminution of the endogenous creatinine clearance. In the "azotemic" group 10 series of determinations were performed.

### RESULTS AND DISCUSSION

In the "normal" group, body weight varied from 51.4 to 97.4 kg. No dosage adjustment was made, in order to simplify the clinical application of our data, because we expected other factors (regularity of dose, intestinal absorption, etc.), for which no correction could be made, to influence the attained urinary sulfadimetine concentration. Actually, as indicated in table 1, the observed free urinary sulfadimetine concentrations were higher in the heaviest subject than

TABLE 1. *Free urinary sulfadimetine concentration attained in individuals of widely different weight with normal renal function*

| BODY WT.<br><br>kg. | FREE URINE SULFADIMETINE CONCENTRATION MC% |                   |                   |                   |
|---------------------|--------------------------------------------|-------------------|-------------------|-------------------|
|                     | 7 a.m. to 12 noon                          | 12 noon to 5 p.m. | 5 p.m. to 10 p.m. | 10 p.m. to 7 a.m. |
| 97.4                | 41.4                                       | 62.2              | 36.2              | 33.5              |
| 51.4                | 18.4                                       | 28.5              | 29.4              | 26.6              |

TABLE 2. *Free urinary sulfadimetine concentration attained in "normal" and "azotemic" groups with dose of 0.125 g. four times a day*

|                 | BODY WT.<br><br>kg. | SERUM<br>CREATININE<br>CONC.<br><br>mg% | ENDOGENOUS<br>CREATININE<br>CLEARANCE<br>% NORMAL | FREE SERUM<br>SULFADIMETINE<br><br>mg% | FREE URINE SULFADIMETINE CONCENTRATION MC% |                      |                      |                      |
|-----------------|---------------------|-----------------------------------------|---------------------------------------------------|----------------------------------------|--------------------------------------------|----------------------|----------------------|----------------------|
|                 |                     |                                         |                                                   |                                        | 7 a.m. to<br>12 noon                       | 12 noon to<br>5 p.m. | 5 p.m. to<br>10 p.m. | 10 p.m. to<br>7 a.m. |
| "Normal".....   | 71.7                | 1.25                                    | 92                                                | 2.81                                   | 26.3                                       | 30.9                 | 24.4                 | 25.0                 |
| (range).....    | (51.4-97.4)         | (1.05-1.43)                             | (88-153)                                          | (1.59-4.73)                            | (11.2-44.2)                                | (9.8-62.2)           | (4.3-44.2)           | (7.1-42.6)           |
| "Azotemic"..... | 54.8                | 5.90                                    | 18                                                | 6.07                                   | 12.0                                       | 14.7                 | 11.3                 | 12.5                 |
| (range).....    | (46.0-65.3)         | (2.49-11.81)                            | (5-35)                                            | (3.65-10.0)                            | (6.4-22.6)                                 | (8.4-23.2)           | (6.2-14.0)           | (6.6-23.0)           |

in the lightest subject. The highest free sulfadimetine concentrations were observed in the specimens collected from 12 noon to 5 p.m., with insignificant differences observed in the other specimens (table 2). In a total of 48 specimens, 16 had a free sulfadimetine concentration of more than 30 mg. per cent and in only 4 was the concentration less than 10 mg. per cent. The mean free serum sulfadimetine concentration was 2.81 mg. per cent.

The observed free urinary sulfadimetine concentration was significantly lower in the "azotemic" group. As in the "normal" group, there was no relationship between body weight, which varied from 46.0 to 65.3 kg., and the free urinary sulfadimetine concentration. Likewise, the highest free sulfadimetine concentrations were observed in the specimens collected from 12 noon to 5 p.m. However, in this group, with a total of 40 specimens, none had a free sulfadimetine concentration over 30 mg. per cent, while 11 had a concentration less than 10 mg. per cent, although none were less than 5 mg. per cent (table 2). In this group the mean free serum sulfadimetine concentration was 6.07 mg. per cent.

As previously mentioned, Helmholtz<sup>2-5</sup> found that sulfathiazole gave satisfactory bacteriostasis with most urinary pathogenic organisms in vitro when the sulfathiazole concentration ranged from 10 mg. per cent to 30 mg. per cent. The present results indicated that such a sulfadimetine concentration can be obtained in bladder urine with the dose of 0.125 g., given 4 times a day, without regard to body size in the adult. Current indications are that sulfadimetine has a similar range of clinical effectiveness to sulfathiazole,<sup>12</sup> and our experience confirms the reported data.

In azotemic individuals a significant number of urine specimens did not reach the desired range of sulfadimetine concentrations on the dosage schedule used. This may be due, in part, to the diminished capacity to concentrate the urine. However, acetylation appears to be increased significantly in azotemic individuals, and this also reduces the effective free sulfadimetine concentration.

#### SUMMARY

Individuals with normal renal function and with impaired renal function and azotemia due to chronic pyelonephritis were given sulfadimetine on the low dosage schedule recommended by Helmholtz and Addis. With normal renal function, even the low total sulfonamide dose of 0.500 g. per day gave a sustained, effective therapeutic concentration in bladder urine. When renal function was impaired, acetylation was increased and the desired free urinary sulfonamide concentrations were nearly but not quite adequately maintained on this dosage schedule.

<sup>12</sup> Gsell, O.: *Schweiz. med. Woch.*, 74: 1095, 1944.



## XYLOCAINE AS A TOPICAL ANESTHETIC IN UROLOGY

LESTER PERSKY AND HAMILTON S. DAVIS

*From the Departments of Urology and Anesthesiology, University Hospitals of Cleveland, Western Reserve University School of Medicine, Cleveland, O.*

In the search for a satisfactory local anesthetic, recent investigations<sup>1, 2, 3</sup> have included a study of Xylocaine, a basic anilide with analgesic action first introduced to the medical profession by Lofgren and Lundquist<sup>4</sup> in 1946. Additional observations revealed the efficacy of the drug in general surgery, dentistry and obstetrics.<sup>1, 2, 5, 6</sup> Moreover, favorable results have been achieved using it as a topical agent in a variety of procedures, such as bronchoscopy, endotracheal intubation and the application of dental prostheses.<sup>7, 3</sup> The employment of Xylocaine topically in urology was first described by Haines and Grabstald<sup>8</sup> who, in a series of 250 cases, found it to be effective. The absence of irritative effects following topical usage had previously been shown by application of an 8 per cent solution to the conjunctival sac of rabbits.<sup>9</sup> More recently, Southworth and Dabbs<sup>10</sup> have used a 4 per cent solution in 190 cystoscopies without reaction.

In an effort to further evaluate its clinical efficacy, the drug has been employed routinely for the past year in this clinic in all cystoscopic examinations and procedures, except in those instances in which general anesthesia was specifically indicated. The degree of success and the incidence of failure and untoward reactions has been studied and constitute the basis of this report.

### MATERIAL AND METHODS

All patients undergoing cystoscopy were utilized in this study. Emotional instability, apprehension or previous failure with other forms of topical anesthesia did not influence the use of the method. General or conduction anesthesia was employed where extreme youth or extent of procedure mitigated against the use of a topical anesthetic.

<sup>1</sup> Gordh, T.: Clinical experience with Xylocaine. *Svensk Lakartidn*, 45: 117, 1948.

<sup>2</sup> Gordh, T.: Xylocaine, a new local analgesic. *Anaesthesia*, 4: 4, 1949.

<sup>3</sup> Hanson, I. R. and Hingson, R. A.: The use of Xylocaine, a new local anesthetic, in surgery, obstetrics and therapeutics. A preliminary report. *Curr. Res. in Anes. & Anal.*, 29: 136, 1950.

<sup>4</sup> Lofgren, N. and Lundquist, B.: Studies on local anesthetics II. *Svensk. Kem. Tidskr.*, 58: 206, 1946.

<sup>5</sup> Bremer, G., Ekmanner, S., Persson, H. and Strandberg, N.: Xylocaine, a new local anesthetic. *Brit. Dental J.*, 85: 278, 1948.

<sup>6</sup> Flowers, C. E., Jr., Hellman, L. M. and Hingson, R. A.: Continuous peridural anesthesia and analgesia for labor, delivery and caesarian section. *Curr. Res. in Anes. & Anal.*, 28: 181, 1949.

<sup>7</sup> Crawford, O. B., Brasher, C., Ottosen, P. and Buckingham, W. W.: Xylocaine, a new local anesthetic agent. *South. Med. J.*, 44: 1073, 1951.

<sup>8</sup> Haines, J. S. and Grabstald, H.: Xylocaine, a new topical anesthetic in urology. *J. Urol.*, 62: 901, 1949.

<sup>9</sup> Goldberg, L.: Pharmacological properties of xylocaine. *Svensk Tandlak-Tidskr.*, 40: 819, 1947.

<sup>10</sup> Southworth, J. L. and Dabbs, C. H.: Xylocaine, a superior agent for conduction anesthesia. To be published.

Premedication consisted for the most part of Demerol, 75 or 100 mg., intramuscularly, approximately 30 minutes before cystoscopy. A barbiturate was employed in addition in less than 10 per cent of the cases.

Routinely, 10 cc of 2 per cent Xylocaine solution was instilled into the male urethra and retained by means of a penile clamp. Roughly five to ten minutes were allowed to elapse before the procedure was begun. In females, a cotton tipped applicator moistened with Xylocaine was placed just within the urethral meatus for a similar length of time. In several instances, where extensive fulguration was anticipated, 20 to 30 cc (400 to 600 mg.) of the drug were instilled

TABLE 1

*Cases*

|                                                                                             |     |
|---------------------------------------------------------------------------------------------|-----|
| Female patients                                                                             | 259 |
| Male patients                                                                               | 363 |
|                                                                                             | —   |
| Total cases                                                                                 | 622 |
| <i>Cystoscopic procedures</i>                                                               |     |
| Observation of bladder only                                                                 | 347 |
| Ureteral catheterization and retrograde pyelography                                         | 343 |
| Biopsy                                                                                      | 30  |
| Fulguration                                                                                 | 45  |
| Miscellaneous                                                                               | 39  |
|                                                                                             | —   |
| (Evacuation of clots, manipulation of calculi, urethral and ureteral dilatation, et cetera) |     |
| Total                                                                                       | 804 |

TABLE 2. *Extensive procedures*

|                                               |    |
|-----------------------------------------------|----|
| Fulguration                                   | 45 |
| Evacuation of clots                           | 11 |
| Manipulation of calculi                       | 7  |
| Transurethral resection of urethral papilloma | 1  |
|                                               | —  |
| Total                                         | 64 |

into the bladder. In this group no toxic reactions were encountered. Eight hundred four procedures were performed on 622 patients; these are listed in table 1. The more extensive procedures in this series are indicated in table 2.

## RESULTS

In all but nine of the cystoscopies, successful completion of the procedure was carried out or was terminated for reasons other than discomfort to the patient. Of the 9 failures (roughly 1 per cent), six were attempted urethral catheterizations, two were cases of Hunner's ulcer and one was a tuberculous cystitis. In no instance was any secondary irritative effect demonstrable.

The toxicity of this new compound has been adequately studied by others;<sup>3, 9, 11</sup> a low relative toxicity in animals and a low incidence of local and constitutional side effects in man were found. In our series only one minor toxic reaction was

<sup>11</sup> Gruber, L. W.: New fields of application for Xylocaine as applied to dentistry. *Oral Surg*, oral Med. and Oral Path, 5: 281, 1952.

encountered. This patient underwent an observation cystoscopy with a transient period of hypotension, pallor and sweating following termination of the procedure. No discomfort was noted during the cystoscopy and, technically, it was atraumatic. Although it is not certain that Xylocaine was responsible for this short-lived episode, it was felt it could not be excluded since subsequent electrocardiographic and laboratory studies failed to demonstrate any other cause. However, *it could have been simple syncope.*

Of interest is the number of procedures for which general anesthesia might ordinarily have been employed (table 2). Initially, topical anesthesia alone was used with some misgivings, and with general anesthesia equipment at hand. The results were so successful, that subsequently the patients were scheduled for topical anesthesia only with no fear of inadequate analgesia. Some of these patients had previously had urethral instrumentation with other forms of topical anesthesia, and volunteered the information that the anesthetic effects of Xylocaine were far superior to any other previously employed agent.

Our results with the use of 2 per cent Xylocaine, a topical anesthetic for cystoscopy are in accord with other investigators. We have found it to be a safe, rapid and adequate anesthetic agent for this purpose.

## A PRACTICAL APPARATUS FOR URINARY INCONTINENCE

R. CARL BUNTS

*From the Department of Urology, McGuire V. A. Hospital, Richmond, Va.*

Those of us who must treat a large number of patients with incontinence such as that seen in the paraplegic are constantly seeking a means whereby we may control incontinence without the use of an indwelling catheter.

The various clamps and other appliances such as the standard rubber bag urinals and the so-called "Texas Special" (condom taped to penis with tube drainage) have several disadvantages, such as, constriction of the skin and deeper tissues of the penis and urethra by clamps, the necessity of wearing a cumbersome and unwieldy urinal or adhesive tape excoriations.

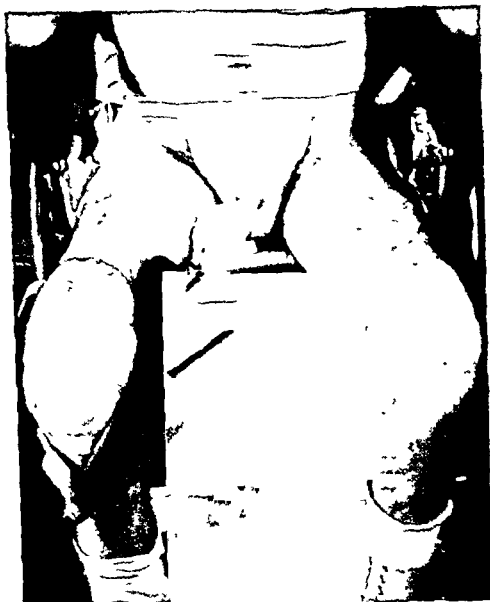


FIG. 1

One of our urological technicians, Mr. Philip Brubaker, aided by the suggestions of incontinent paraplegic patients, has devised a simple apparatus which has been most satisfactory in the care of paraplegic and other patients with a true or pseudo incontinence. It has been found to be "water tight" even though the patient be in a sitting or prone position and may be used with or without the lower leg bag extension (fig. 1).

This apparatus has been constructed by sewing a Davol or Bard urinal top to the central portion of an athletic supporter beneath the waist band. This appliance is now manufactured by the C. R. Bard Co. and is to be listed in their catalogue as "The McGuire Urinal."

Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

Accepted for publication October 6, 1952.

PROGRAM, ANNUAL MEETING OF NORTHEASTERN SECTION,  
AMERICAN UROLOGICAL ASSOCIATION, SHAWNEE  
ON DELAWARE, PA., SEPTEMBER 15-18, 1953

SEPTEMBER 16, 1953

OSTEITIS PUBIS, Dr. Julius Gelber, Schenectady, N. Y.

VESICORECTOSTOMY THROUGH ITS FIRST FIVE YEARS, Dr. Joseph G. Moore, Pittsburgh, Pa.

PRIMARY CARCINOMA OF THE URETER, Dr. J. Victor Berry, Ottawa, Canada

RADICAL SURGERY AND CARCINOMA OF THE KIDNEY, Dr. Howard T. Thompson, Rochester, N. Y.

A NEW TECHNIQUE OF PROSTATIC ADENOMECTOMY, Dr. J. P. Bourque, Montreal, Canada

THE NORMAL AND ABNORMAL PHYSIOLOGY OF THE ADRENAL CORTEX, Dr. Dalton Jenkins, Boston, Mass.

NEW CALCULUS EXTRACTOR, Dr. Benjamin Levant, Pittsburgh, Pa.

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PROGRESS REPORT ON THE USE OF INTERSTITIAL RADIATION IN CARCINOMA OF THE PROSTATE, Dr. Rubin H. Flocks, Iowa City, Iowa.

THE LATE RESULTS OF THE RADICAL OPERATION FOR CARCINOMA OF THE PROSTATE, Dr. J. A. Campbell Colston, Baltimore, Md.

IMPORTANCE OF VAGINITIS IN URINARY INFECTIONS OF CHILDHOOD, Dr. Raymond Stept, Pittsburgh, Pa.

SURGICAL APPROACH FOR URINARY INCONTINENCE IN A SPINA BIFIDA CHILD, Dr. R. A. Hancock, Pittsburgh, Pa.

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THE CRUSH KIDNEY SYNDROME. A NEW CONCEPT, Dr. W. G. Bigelow, Toronto, Canada

ROLE OF URINARY COLLOIDS IN THE ETIOLOGY AND MANAGEMENT OF UROLITHIASIS, Dr. Arthur J. Butt, Pensacola, Fla.

THE MEDICAL MANAGEMENT OF ACUTE AND CHRONIC RENAL FAILURE, Dr. Dalton Jenkins, Boston, Mass.

THE EFFECT OF ORALLY ADMINISTERED BETA-NAPHTHYLAMINE ON NORMAL AND ISOLATED SIGMOID-LOOP, SUBSTITUTION BLADDERS IN DOGS, Dr. Winfield W. Scott, Rochester, N. Y.

THE USE OF AN ISOLATED SEGMENT OF ILEUM AS A CONVEYOR OF URINE, Dr. William C. Baum, Ann Arbor, Michigan.

PROGRAM. ANNUAL MEETING OF NORTH CENTRAL SECTION,  
AMERICAN UROLOGICAL ASSOCIATION.  
CINCINNATI, O., OCTOBER 8-10, 1953

- BASIC SCIENCE LECTURE THE USE OF RADIOACTIVE ISOTOPES IN MEDICINE. Otto Glasser (by invitation). Cleveland, Ohio
- PRESENT STATUS OF RADIOACTIVISOTOPES IN TREATMENT OF CARCINOMA OF THE PROSTATE AND BLADDER, Vincent J. O'Connor, Chicago, Ill.
- GUEST SPEAKER, BASIC SCIENCE LECTURE ELECTROMYOGRAPHY IN THE STUDY OF THE URINARY BLADDER, E. L. Corey (by invitation). Charlottesville, Va.
- BASIC SCIENCE LECTURE BASIC ENDOCRINOLOGY OF MALE TESTICULAR DEFICIENCY, A. Albert (by invitation), Rochester, Minn
- BASIC SCIENCE LECTURE FLUID AND ELECTROLYTE BALANCE C. D. Creevy, Minneapolis, Minn
- PRESIDENTIAL ADDRESS William J. Engel, Cleveland, Ohio
- HONORARY GUEST SPEAKER ADRENAL TUMORS George F. Cahill, New York, N. Y.
- A SIMPLIFIED BASIC TECHNIQUE FOR URINE CULTURE. John W. King and Alfred Reich. (by invitation), Cleveland, Ohio
- LEIOMYOSARCOMA OF THE URINARY BLADDER. Sidney J. Silbar and John D. Silbar (by invitation) Milwaukee, Wis
- RETENTION OF FERTILIZING CAPACITY OF HUMAN SPERMATOZOA STORED AT LOW TEMPERATURES. R. G. Bunge, Iowa City, Iowa
- INTERSTITIAL CISTITIS A CAUSE OF PERSISTENT BLADDER DISABILITY, William J. Baker and Edwin C. Graf, Chicago, Ill
- CARCINOMA OF THE FEMALE URETHRA, Arthur A. Roth, Cleveland, Ohio
- RENAL PAPILLARY NECROSIS, A CLINICO-PATHOLOGIC STUDY. Robert A. Garrett and (by invitation) Max S. Norris and Frank Vellios, Indianapolis, Ind
- PRIMARY MEGALO URETER. Reed M. Nesbit, Ann Arbor, Mich
- TORULOSIS OF THE PROSTATE. Sidney P. Hurwitz, E. B. Jacobson and (by invitation) I. I. Kolman Milwaukee, Wis
- THE MORPHOLOGICAL AND PHYSIOLOGICAL DEVELOPMENT OF THE KIDNEY BETWEEN INFANCY AND PUBERTY. Frank B. Bicknell, Detroit, Mich
- URETHRAL DIVERTICULUM IN WOMEN. Edward N. Cook, Rochester, Minn
- PANEL DISCUSSION NEWER DIAGNOSTIC METHODS IN UROLOGY (SPECIAL TECHNIQUES IN EXCRETORY UROGRAPHY NEPHROTOMOGRAPHY, AORTOGRAPHY, PRESACRAL PNEUMOGRAPHY et cetera)
- Moderator James C. Sargent, Milwaukee, Wis
- Discussors Edgar A. Webb, Minneapolis, Minn
- Arthur T. Evans, Cincinnati, Ohio
- James W. Merricks, Chicago, Ill
- E. F. Poutasse (by invitation) Cleveland, Ohio
- PYELOGRAPHIC CLINICS Demonstrators to be announced later

*Brief Topics and Useful Aids (3 Minute Talks)*

- Z PLASTY OR CORRECTION OF MEATAL URETHRAL STRICTURE FOLLOWING HYPOSPADIAS REPAIR Reed M. Nesbit, Ann Arbor, Mich
- THE USE OF SKIN IN NEPHROPEXY. Benjamin H. Brunkow, Monroe, Wis
- A MODIFIED EO-IN-NIGROSIN STAIN FOR SPERMATOZOAL VIABILITY, R. G. Bunge, Iowa City, Iowa
- AN URETHRAL STRICTURE. Arthur A. Roth, Cleveland, Ohio
- METASTATIC CANCER OF THE PENIS E. F. Poutasse (by invitation), Cleveland, Ohio

- MALIGNANT TESTICULAR TUMOR MANIFESTING TRANSILLUMINATION, Paul J. Schildt, Lakewood, Ohio
- MANIPULATION OF URETERAL CALCULI—MEATOTOMY AND IMMEDIATE DELIVERY, Joseph H. Kiefer, Chicago, Ill.
- ECONOMICS AND ELECTRONICS, Albert P. Graham, Neenah, Wis.
- SIMPLE RENAL CYSTS IN THE NEW BORN: REPORT OF TWO CASES, William W. Christeson (by invitation), Detroit, Mich.
- ELEPHANTIASIS OF THE PENIS: A CASE REPORT, John H. O. Mertz, Indianapolis, Ind.
- METHOD OF THREADING RADIUM IN CATHETER FOR WALTER REED RADIATION TECHNIQUE, Robert S. Breakey, Lansing, Mich.
- CONTROL OF PROFOUND HEMATURIA RESULTING FROM UNCONTROLLED OVERDOSE OF DICUMEROL, Robert S. Breakey, Lansing, Mich.
- SUPRAPUBIC CYSTOSTOMY OF LOWER AND ENGEL, Francisco Barquin (by invitation), Havana, Cuba
- SARCOMA OF THE PROSTATE: AN UNUSUAL SURVIVAL, Richard S. Graves, Dayton, Ohio

# ERRATUM

August 1953 issue, p. 338. Senior author's last name is Nangle, not Nagle





## THE PLACE OF THE ARTIFICIAL KIDNEY IN RESEARCH AND TREATMENT

J. HARTWELL HARRISON

*From the Surgical and Medical Services of the Peter Bent Brigham Hospital, and Department of Surgery of the Harvard Medical School, Boston, Mass.*

The activating stimulus to carry out an investigation of the artificial kidney at the Peter Bent Brigham Hospital was the visit of W. J. Kolff<sup>1</sup> to that institution more than five years ago. The immediate possibilities of the value of such a tool in the study and treatment of renal insufficiency seemed very real. To Drs. George W. Thorn and John P. Merrill of the Medical Service and Carl W. Walter of the Surgical Service we are indebted for the initiation and expediting of an extensive program involving external dialysis applied to the experimental animal and to the anuric patient during the last four years. Dr. Merrill and his associates of the Renal Group, Medical Service, have devoted themselves completely to the study of the pathologic physiology and treatment of renal insufficiency with all of its various ramifications and broad implications. The Urologic Service has enjoyed the privilege of participating in this program in both a diagnostic and therapeutic capacity. The success of the program has depended upon numerous factors prominent among which has been the constant and close cooperation of personnel of both the Medical and Surgical Services.

It is the endeavor of this communication to present the objective evaluation of one who has participated in this venture as a clinical consultant but who has not been primarily identified with this project. One sees in this program the utilization of a new and complex apparatus that employs certain simple principles of physical chemistry which determine the transfer of substances across an inert membrane. Real analogies may be found in both plant and animal life in the transfer that occurs across vital membranes. Dr. Merrill<sup>2</sup> has compared the pores of the dialyzing membranes of cellophane with the vital membranes of muscle and glomerular capillaries. The mean pore radius of cellophane used in the artificial kidney is about 30 Angstrom units and the fractional pore area (dialysis surface) of cellophane available for transfer varies from 30 to 45 per cent. The total dialyzing area of the Kolff apparatus is 22,000 square cm. of cellophane. The glomerular capillary has a fractional pore area of 0.01 per cent and the total area of the human glomerular capillaries has been estimated at 7600 to 15,000 square centimeters. This comparison concretely gives one an idea only of the physical potentials of the artificial kidney.

Read at annual meeting, North Central Section, American Urological Association, Minneapolis, Minn., October 9, 1952.

<sup>1</sup> Kolff, W. J. and Berk, H. T. J.: Artificial kidney; dialyzer with great area. *Acta med. Scand.*, 117: 121-134, 1944.

Kolff, W. J.: Artificial kidney. *Cleveland Clinic Quart.*, 17: 216-228, 1950.

<sup>2</sup> Merrill, J. P.: Medical progress: The artificial kidney. *New Eng. J. Med.*, 246: 17-27, 1952.

Merrill, J. P.: The use of the artificial kidney. *Transactions of the Third Conference: Renal Function*. Pp. 139-173. Josiah Macy Jr. Foundation.

There has been the inevitable controversy which follows the introduction of new methods and new techniques. Simultaneously with the development of external dialysis there has been a great improvement in the conservative methods of management of renal failure as discussed by Dr. Lewis today. It seems without question that external dialysis is a definite supplement to the established therapeutic armamentarium; it goes parallel to the latter but further in attaining a greater potential for quickly correcting electrolyte disturbances and retention of metabolites. The use of intestinal lavage and drainage has been efficacious but characterized by definite limitations. The same may be said of peritoneal dialysis. The use of an isolated loop of small intestine as a dialyzing membrane as described by Creevy has yielded impressive results and deserves further investigation and use. The effectiveness of a vital membrane as over against an inert membrane demands more exploration.

Multiple efforts at simplification and improvement of the artificial kidney have been undertaken by Kolff,<sup>1</sup> Alwall,<sup>3</sup> Murray,<sup>4</sup> Skeggs and Leonards,<sup>5</sup> Murphy,<sup>2</sup> and Rosenack.<sup>2</sup> Two separate functions have been served by the various types of artificial kidney in use at the present as pointed out by Dr. Swann. When the use is made of the fact that the cellophane membrane is impermeable to colloidal solids but passes water and crystalloids the mechanism is one of only dialysis as carried out in the apparatus of Kolff. If the hydrostatic gradient is converted to a hydrodynamic gradient across the membrane by increase of pressure within the the supported membrane there results a process of filtration. Merrill<sup>2</sup> has pointed out that the problem of mechanical design stressed so much in the literature may not be so important as the modification of the membrane itself and an attempt to regulate the pore size to meet specific requirements as a dialyzing membrane. This will undoubtedly constitute an important aspect of the research program of the future.

#### THE ADVANTAGES AND DISADVANTAGES OF THE ARTIFICIAL KIDNEY

It seems appropriate to summarize briefly what can be accomplished by means of external dialysis. In a study of renal insufficiency the availability of such an instrument has quickly resulted in the referral of many patients suffering from oliguria or anuria from various causes in whom conservative methods of management had apparently failed. At first these patients were sent to Dr. Merrill from local hospitals but as the efficacy of the therapy was realized the sources of material for study were hospitals throughout New England and subsequently from many parts of the United States. Support for the project was rendered by the United States Army and for some months now an artificial kidney has been operated by a team in a hospital in Korea. Many of the patients who have been referred for treatment have been managed successfully without external dialysis. The Urologic Service has been aware of the increased

<sup>1</sup> Alwall, N.: On the artificial kidney: Apparatus for dialysis of blood in vivo. *Acta med. Scandinav.*, 128: 317, 1947.

<sup>4</sup> Murray, G.: Development of artificial kidney; experimental and clinical experiences. *Arch. Surg.*, 55: 505, 1947.

<sup>5</sup> Skeggs, L. T., Jr. and Leonards, J. R.: Studies on artificial kidney; preliminary results with new type of continuous dialyzer. *Science*, 108: 212, 1948.

number of patients having renal insufficiency in the hospital population because of the increasing number of consultations, diagnostic procedures and operations necessary on this type of patient. Statistics compiled at a large academic institution in a neighboring metropolis where this program has been felt to be perhaps unnecessary showed that in 22 years only 37 patients with anuria or oliguria of 100 cc or less per day for 3 days had been treated. This would indicate that the demand for such an apparatus is relatively very infrequent and certainly not enough to justify that every large hospital have such therapy available. Our observations would concur with this deduction at the present time. However, in 4 years at the Peter Bent Brigham Hospital with a bed capacity of less than 300, more than 290 clinical trials with the artificial kidney on 175 patients have been carried out and no deaths have occurred as a result of the procedure. The great majority of these patients have been sent to the hospital specifically for dialysis or for treatment by the renal group. Those who have been sent and treated without dialysis have more than equaled in number those who have received this therapy. This experience answers one of the questions which prompted Dr. Nesbit to request that this symposium be undertaken, namely, that there is a definite demand today for the artificial kidney. To qualify the answer by stating how many are needed in this country today is impossible at the present. Further experience both of an investigative and therapeutic nature in other sections of the country will be necessary in order to determine the actual demand. It certainly will not become apparent until it is more easily available in different sections. The work of Dr. Keitzer in Akron is extremely significant and certainly opens new possibilities for the expansion of the project to ascertain the usefulness of and demand for the artificial kidney. One visualizes, however, at the present primarily the establishment of this method of investigation and treatment of renal insufficiency in designated institutions wherein there are groups sufficiently interested to expedite a program and to whom adequate facilities are available to evaluate completely the results obtained. External dialysis as first performed by Abel, Rowntree and Turner<sup>6</sup> in 1913 using collodion as a membrane and hirudin as an anticoagulant has made great progress owing to its revival by Kolff in 1944 and continued use and improvements by several investigators.

In the absence of an obstructive lesion in the urinary passages the electrolyte imbalance of acute renal insufficiency can be more quickly and safely corrected by external dialysis probably than by any other method available today. If anuria persists, further dialysis will be necessary. The selective removal of electrolytes and metabolites is accomplished in a period of 6 hours or less. The restoration of normal acid-base balance is accomplished by the replacement of desirable cations. The removal of potassium occurs rapidly and temporarily corrects the intoxication which may cause myocardial inhibition and death. Improvement of the chronic uremic patient from a state of torpor to wakefulness and ability to take nutrition has been impressive. Unquestionably there

<sup>6</sup> Abel, J. J., Rowntree, L. G. and Turner, B. B.: On removal of diffusible substances from circulating blood by means of dialysis. *Trans. Assoc. Amer. Col. of Phys.*, 28: 51-54, 1913.

has been a shortening of hospitalization for many patients with both acute and chronic renal failure. In selected cases of renal insufficiency where mandatory surgery is to be done it is possible to improve the patient's condition by pre-operative dialysis and also there is simultaneously the security of aid from dialysis postoperatively, if it is needed. This security in fact has encouraged us to carry out necessary definitive surgery on patients who would have otherwise received conservative and palliative measures e.g. constant drainage of the bladder, ureteral catheter drainage, ureterostomy or nephrostomy. The quick improvement of anuric or oliguric patients or even the chronic uremic after dialysis indicates that the important excretory mechanisms have been taken over in large part effectively though temporarily. Chinard<sup>2</sup> has proposed the possibility that nitrogen compounds other than urea and uric acid (e.g. the nitrous acids) may be removed from the circulation of the uremic patient with beneficial effect.

Increased cardiac output during dialysis has been shown by Dexter to occur if the patient has an able myocardium. Also an increase of peripheral resistance in the hypertensive patient has been found to occur as manifested by regaining a normotensive state if he was in shock before. The profound hypotension at times complicating biliary surgery has been successfully combated by external dialysis; this has been interpreted to indicate the removal of a toxic substance (V.D.M.) which the liver could not break down. This is perhaps a catabolic product of protein metabolism. It is significant that amino-acid nitrogen can be reduced to normal by dialysis but an apparent homeostatic mechanism comes into play which prevents a fall to subnormal levels.<sup>2</sup>

As has been emphasized repeatedly external dialysis is reserved for those patients who have not responded to conservative therapy. It is not a panacea for anuria and does not replace any standard form of therapy or surgical drainage of obstructive lesions by catheter or scalpel. It must be regarded as a supplement to other accepted forms of treatment. The disadvantages militating against its use are several. It is a highly specialized, complicated and expensive apparatus still in an investigational stage of development. It is yet desirable to have a trained team to operate it and to care for the patient. Many personnel hours can be expended in preparation and operation. Simplification and improvements will undoubtedly correct much of this. Hypertensive episodes during analysis may be hazardous and furnish a contra-indication in the case of patients having hypertensive vascular disease, coronary thrombosis and acute glomerulonephritis. The necessity for heparinization makes gastro-intestinal bleeding a contra-indication to its use. Hemorrhage during dialysis may occur into the gastro-intestinal tract and intracranial bleeding is an infrequent but serious complication again to be feared especially in the hypertensive patient. The increased cardiac output produced furnishes a contra-indication for the patient in acute myocardial failure. Increased peripheral resistance which occurs is undesirable in the anuric patient who is hypertensive. Too rapid correction of the chemical abnormalities may induce cardiac arrhythmia because of the sudden fall in serum potassium and rise in sodium and calcium. The hazard of overhydration

of the patient or of excessive dehydration must be guarded against and also excessive hyperglycemia may result if the respective milliosmols of the bath and circulation are not balanced properly.<sup>2</sup> On the basis of a review of the literature and a careful appraisal of the work at the Peter Bent Brigham Hospital during the last 4 years, it is concluded that the advantages and benefits derived from the artificial kidney far outweigh the disadvantages, complications and hazards of such therapy in properly selected patients. We have been especially impressed with the value of external dialysis for the anuric patient suffering from acute primary failure of renal excretion who is tided over a critical period until circulatory and tubular regenerative factors result in resumption of renal function. The remarkable regenerative potentiality of the kidney after toxic and traumatic insult confers a concrete value to the artificial kidney.

#### ABSTRACTS OF CLINICAL EXAMPLES

L. B. Age 43. Female. No. 9A836. Admitted to the Medical Service March 14, 1949 because of anuria, chronic pyelonephritis, nephrolithiasis left, p.o. nephrectomy, right, ? post transfusion reaction. Third hospital day external dialysis with following chemical changes: B.U.N. 84-24 mg. %; N.P.N. 116-54 mg. %; CO<sub>2</sub> 19-21.6 mM/l; chlorides 101-114 mEq/l; NA 132-133 mEq/l; potassium 4.3-4.4 mEq/l; phosphorus 1.7-0.7 mEq/l; calcium 5.7-7.1 mEq/l. An excellent clinical result was obtained with marked improvement. In one week the urinary output was 1800 cc. The patient was not in acidosis again. B.U.N. gradually, after a preliminary rise to 60 mg. %, returned to normal in 2 weeks. The patient was discharged 1 month later.

Two months later the patient was readmitted and exploration revealed the presence of a parathyroid adenoma which was removed. This patient illustrates the quick rehabilitation from a debilitating state of severe renal failure by external dialysis which led to recovery and the possibility of removal of a parathyroid adenoma.

D. K. Male. Age 72. No. 7B568. Admitted to the Medical Service October 9, 1950. Diagnosis: Anuria due to intravascular hemolysis following transurethral prostatectomy elsewhere with distilled water. The patient was anuric. Hematocrit 32; B.U.N. 87 mg. %; CO<sub>2</sub> 18 mM/l; chlorides 89 mEq/l; Potassium 5.4 mEq/l.

External dialysis 4 days after admission October 13, urinary output 185 cc. Two days later 1000 cc and progressive diuresis occurred. Following changes occurred during dialysis: B.U.N. 118-52.6 mg. %; CO<sub>2</sub> 10.3-15.5 mM/l; chlorides 89-110 mEq/l; sodium 128-140 mEq/l; potassium 5.9-4.9 mEq/l; Hct. 26-35; calcium 3.3-6.0 mEq/l.

The patient had shown electrocardiographic signs of potassium intoxication prior to dialysis. He did well after dialysis for 2 days and then went into collapse, was transfused and exploration carried out for mesenteric thrombosis but a ruptured aneurysm of the left hepatic artery was found. The postoperative course was satisfactory and he was discharged 3 weeks later. Exploration resulted in successful suturing of a rent in the hepatic artery by Dr. David Hume.

This case is illustrative of how soon successful major surgery may be carried out upon a patient after external dialysis.

E. B. Male. Age 56. No. 8B154. Admitted to the Medical Service January 24, 1951. Diagnosis: sulfadiazine anuria, four days' duration.

P. E. Shock-like state with severe dehydration. Chemistries: B.U.N. 149 mg.%; CO<sub>2</sub> 21.5 mM/l; sodium 144 mEq/l; potassium 5.5 mEq/l; sulfa level 21.8 mg.%. External dialysis January 26 followed by chemistries: B.U.N. 68 mg.%; chlorides 109 mM/l; sodium 144 mEq/l; potassium 4.9 mEq/l; sulfa 13.6. Six days later chemistries: B.U.N. 73 mg.%; CO<sub>2</sub> 19.6 mM/l; chlorides mEq/l; sodium 140 mEq/l; potassium 4.3 mEq/l; phosphorus 7.7 mEq/l, previously 2.7 mEq/l; sulfa 3.8.

Subsequently cystoscopic examination showed the right kidney to be non-functioning and a very large opacity was present in the region of the right lower ureter thought to be a ureteral calculus. The patient's condition improved during the month following external dialysis with B.U.N. 20 mg.%; CO<sub>2</sub> 20 mM/l; chlorides 105 mEq/l with a good urinary output and concentration 1027.

Operation was performed to remove a large ureteral calculus. The kidney continued to be nonfunctioning and a right nephro-ureterectomy was carried out. Diagnosis: Renal cell carcinoma.

Convalescence was uneventful. Fourteen months later appendectomy for acute appendicitis. Convalescence was uneventful. This case illustrates the successful treatment of acute sulfadiazine anuria which permitted subsequent removal of a renal neoplasm.

D. B. Male. Age 56. No. 9A387. Admitted in September 1946 with chronic pyelonephritis, urinary retention, severe azotemia and acidosis due to stricture of the urethra. Hospitalization for 3 months with drainage of the bladder and gradual dilatation of the urethral stricture were carried out. He did well for 2 years and was re-admitted December 27, 1948 in severe renal failure. External dialysis was performed 1 week later. B.U.N. 93-41 mg.%; N.P.N. 145-53 mg.%; CO<sub>2</sub> 13.2-19 mM/l; chlorides 91-111 mEq/l; sodium 140-140 mEq/l; potassium 4.8-4 mEq/l; phosphorus 1.6-0.5 mEq/l. Clinical improvement was marked. Dilatation of urethral stricture was accomplished in a week. Patient discharged less than thirty days after admission. The striking feature is the quick improvement of the patient and much shorter hospitalization because of external dialysis.

Re-admitted May 12, 1950. External dialysis changes: B.U.N. 114-48 mg.%; N.P.N. 167-51 mg.%; CO<sub>2</sub> 15-18 mM/l; chlorides 90-98 mEq/l; sodium 129-140 mEq/l; potassium 2.6-3.8 mEq/l; phosphorus 2.8-0.8 mEq/l; uric acid 9.4-3.1; calcium 4.9-6.2 mEq/l; uric acid changes are notably outstanding and likewise the diminution in the retained phosphorus. Clinical improvement was excellent in spite of the patient's diminished renal reserve. The quick rehabilitation of a debilitated individual by this method of treatment is very impressive.

A. F. Female. Age 46. No. 9B653. Admitted oliguric, acidotic and azotemic. Right kidney absent 4 years. Left ureter reimplanted in bladder 3 months before because of obstruction by endometriosis.

Chemistries: B.U.N. 132 mg.%; after dialysis 45 mg.%; sugar 95-95; CO<sub>2</sub>

12.7–17.7 mM/l; sodium 128–139 mEq/l; chlorides 95–111 mEq/l; potassium 4–4.2 mEq/l; dialysis was followed by marked clinical improvement. The patient was transferred to surgery and left ureterocutaneous anastomosis carried out. The patient returned to work two months later. The case is illustrative of successful quick preparation of a patient in renal failure for definitive surgery.

L. H. Female. Age 69. No. 6B626. Admitted to the Medical Service April 9, 1950 because of anuria pursuant to collapse following cholecystectomy two days before. The patient had been anuric 8 days upon admission. Forty-eight hours after admission external dialysis was performed. Chemical changes: B.U.N. 98.4–39.3 mg. %; N.P.N. 237–79 mg. %;  $\text{CO}_2$  13.8–19 mM/l; chlorides 102–108 mEq/l; sodium 134–138 mEq/l; potassium 4.3–5 mEq/l; phosphorus 2.9–1.0 mEq/l; urinary output increased daily after dialysis as follows: 290, 600, 1000, 1300, 1500 cc. Dramatic improvement occurred and the patient was discharged fifteen days after dialysis.

L. W. Male. Age 16. No. 9B966. Transferred to Medical Service from neighboring hospital—severe azotemia, oliguria and acidosis, due to bilateral congenital hydronephrosis, chronic pyelonephritis and megaloureter. External dialysis—chemical changes: B.U.N. 160–33 mg. %;  $\text{CO}_2$  13–22 mM/l; chlorides 111–111 mEq/l; sodium 138–140 mEq/l; potassium 4.7–4.8 mEq/l. The patient became ambulatory, was markedly improved and able to eat. He remained at home in an improved condition for 4 months when he was readmitted and dialysis repeated to correct acidosis.

B.U.N. 143–153 mg. %;  $\text{CO}_2$  15–26 mM/l; chlorides 103–106 mEq/l; sodium 137–138 mEq/l; potassium 4.4–4.9 mEq/l; hematocrit 26–25. The patient was improved by this dialysis though the azotemia was not lowered. Eight days later dialysis repeated: B.U.N. 147–44 mg. %;  $\text{CO}_2$  20–26 mM/l; chlorides 105–105 mEq/l; sodium 139–138 mEq/l; potassium 5.6–4.5 mEq/l. The patient was again improved for 2 months. Subsequently he went gradually downhill and died in renal failure. This case illustrated the possibility for prolongation of life in the chronic uremic state where desirable in selected cases.

#### THE ROLE OF THE ARTIFICIAL KIDNEY IN RESEARCH

The artificial kidney seems to have especial promise in the investigation of electrolyte and protein metabolism in various pathologic states among which may be mentioned renal disease, hepatic disorders, shock, burns, hemoglobinemia, drug intoxication and congestive heart failure. This method of study permits an accurate measurement of the exchange of cations, anions and organic solutes e.g. urea, uric acid, creatinin, phenols, indoxyls, sulfonamides and others to be identified.<sup>1</sup> There have been in use for several years smaller models of the artificial kidney (Skeggs and Leonards, and Murphy) adapted to use in the dog for experimental purposes. The ability to remove from the circulation and replace diffusible substances selectively permits a study of the effect of different concentrations of these. For example, the neuromuscular effects of raising the concentration of potassium in the presence of a falling concentration of calcium and the effects upon the electrocardiogram of relative changes in concentrations



of sodium and potassium can be studied. By modification of the membrane it is possible that new potentialities will be developed. A study of amino-acid metabolism in hepatic disorders and when normal liver function is present has been suggested. Further elucidation of the cause of the toxemia in the uremic state is being sought since the combination of catabolic products yielding this state has not been identified. Observations on acute and chronic uremia suggest a possible difference in the manner in which urea is metabolized in these respective conditions. Further information regarding the chemical nature of uremia may be obtained by applying the newer techniques for qualitative analysis e.g. paper chromatography.

The apparent removal of vasodepressor substances has been accomplished but the nature of these is yet to be identified. The application of the use of the radioactive isotopes of both cation and anions as tracers, the total body water studies of Moore and selective dialysis promise to disclose further useful data in renal disease and congestive heart failure. Dexter has measured cardiac output before and during dialysis by means of venous catheterization; further study is indicated of the mechanism of increased cardiac output which occurs. Thorn has suggested the experimental application of the artificial kidney to the study of shock, the crush syndrome and burns as a method of learning more of the nature of the metabolites in the circulation in these conditions. In Korea a study of epidemic hemorrhagic fever is under way in which an application to an infectious disease has been made.

In the field of toxicology one must mention the studies made in the treatment of bromism, sulfonamide intoxication, carbon tetrachloride, barbiturate, and bichloride of mercury poisoning. The effective elimination of diffusible poisons and their by-products as well as the simultaneous substituted renal function has yielded impressive results.

One of the important investigative problems that has grown out of and been made possible by the artificial kidney is that of the homologous transplantation of the human kidney. The recipients of such a transplant have been patients having irreversible renal failure due to pyelonephritis, nephritis, polycystic disease or periarteritis nodosa. Dr. David Hume has carried out seven such transplants in as many patients. Three of these functioned for periods of one to three months, three were failures from the outset and one is yet under evaluation ten days after the operative transplantation. Each of these kidneys was transplanted to the thigh which permitted separate measuring of its function. The one most recently performed was accomplished fifty days after anuria began in a woman aged 60 years; on the fortieth day of anuria, life having been sustained by external dialysis on three occasions, biopsy of the left kidney showed an irreversible condition due to periarteritis nodosa. Now sixty days in an anuric state the patient feels quite well and is yet in electrolyte equilibrium following her fifth dialysis. Her own kidneys are not functioning but the transplanted kidney has begun to excrete urine. The importance of pursuing such an investigation to a finality needs no emphasis. The immunologic, hematologic and bacteriologic problems involved are undergoing intensive investigation. Much

greater success has been met in the human than in the experimental animal with homologous transplantation of both kidney and skin. The artificial kidney has made available a justifiable source of human subjects with fatal renal disease for this study.

#### SUMMARY

The urologist more than any other physician is concerned predominantly with disorders of the kidney. He has the most definitive diagnostic means and effective therapeutic methods at his disposal for the management of certain types of renal disease. However, in the management of patients having severe renal insufficiency the value of external dialysis in preoperative and post-operative care must be recognized. It is necessary that we be conversant with the extraordinary methods developed to study and treat renal disease which surpass our usual limitations. Dr. Keitzer and perhaps others have successfully and alone utilized the artificial kidney for therapy. An attempt has been made to outline what has been accomplished by its use and predictions have been made as to paths of investigation to be followed with its aid in the future. An undoubted demand has been established but its extent remains to be determined.

It is suggested that extension of its use be gradual. At the present stage of development it would seem appropriate if there was one team to each area of this country roughly corresponding in size to each Section of the American Urological Association. Effective research and therapy could be accomplished with the support and cooperation of the Section behind such an investigative group. It is apparent that difficulties will be met in finding medical personnel sufficiently interested to undertake such a project and the problem will require the sustained stimulation of an organized group. It is suggested that this demand be further studied by a joint committee of the American Urological Association, American College of Physicians and American College of Surgeons. A logical sequence of demand and supply could then be determined as a program is developed.

## A NEW URETERAL MEATOME FOR USE WITH THE RESECTOSCOPE

R. G. BUNGE

*From the Department of Urology, University Hospitals, State University of Iowa, Iowa City, Iowa*

This meatome\* is a modification of the cutting loop of the Stern-McCarthy resectoscope and its modifications (fig. 1). Other meatomes, it was found, lacked precise control of the cutting element, others were awkward to use through the cystoscope, and still others were too large to be acceptable to the ureteral orifice.

### URETERAL MEATOME

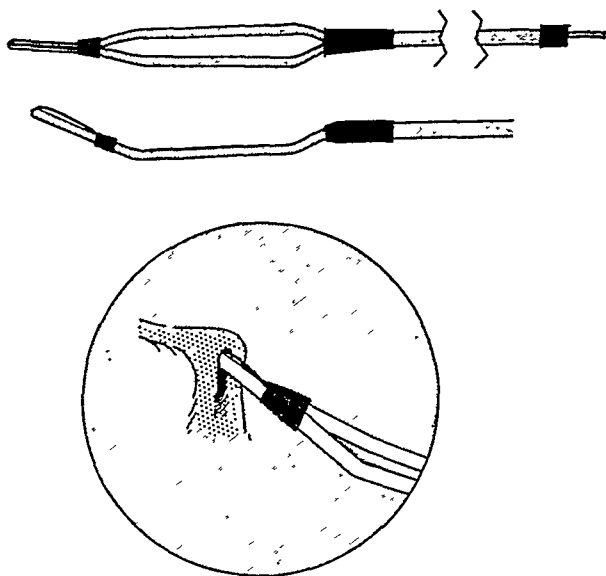


FIG. 1

Replacing the cutting loop with a meatome, the resectoscope is rotated through  $180^\circ$  and then the cutting element assumes an angle for ready insertion into the ureteral orifice. Its small diameter permits ease of insertion. A slight elevation of the electrode while applying the cutting current results in a neat incision of the superior ureteral wall without damage to the opposing inferior wall.

An additional use was discovered in incising the superior wall of the intramural ureter when a stone was impacted near the ureteral orifice. It could be used to correct other surgical conditions of the ureter, such as ureterocele.

\* Manufactured by The Greenwald Co., Inc., Gary, Ind.

## THE PHYSIOLOGY OF HYPERCHLOREMIC ACIDOSIS FOLLOWING URETEROSIGMOIDOSTOMY: A STUDY OF URINARY REABSORPTION WITH RADIOACTIVE ISOTOPES

MILTON L. ROSENBERG

*From the Department of Surgery, Division of Urology, Stanford University School of Medicine,  
San Francisco, Calif.*

The electrolyte imbalance which occurs following bilateral ureterosigmoidostomy was studied by means of radioactive isotopes as tracer substances and by analysis of venous blood directly draining the sigmoid wall. The first phase of the experiments consisted of the rectal instillation of isotopes so that absorption of electrolytes could be measured. Sodium (Na 24), iodine (I 131) and phosphorus (P32) were used. The absorption of chlorine and iodine from the gastrointestinal tract is similar and there is a well-known similarity in the diffusion (except in the thyroid gland) and excretion of these two halogens.<sup>1, 2</sup> I 131 is readily available and its uptake can be measured in the thyroid gland. The second phase of the experiment consisted of comparing the amount of ammonia, chloride and urea and the pH in blood from the sigmoid veins with that in portal and peripheral blood.

### EXPERIMENTAL METHODS AND RESULTS: ABSORPTION OF ELECTROLYTES THROUGH MUCOSA OF SIGMOID

*General techniques and materials.*—In phase one, 27 experiments were carried out using 8 normal dogs as controls and 4 dogs with bilateral ureterosigmoidostomy. All animals were anesthetized with nembutal. Weight of the normal animals was between 8 and 10 kilograms; that of experimental animals was between 10 and 15 kilograms. Prior to operation, every animal in both groups had normal renal function and electrolyte balance. Experiments were carried out from 2 to 6 months after ureterosigmoidostomy. Hyperchloremic acidosis developed in three of the four dogs with transplanted ureters within 2 weeks postoperatively; it developed in the fourth animal after 3 months (table 1).

Isotopes were instilled per rectum and the amount of the isotope in the blood, urine and stool was measured. For I 131, thyroid uptake was also measured. Isotopes were obtained through the Atomic Energy Commission and a Berkeley Decimal Geiger-Muller Scaler, Model 1000, was used to measure the isotope levels. Thyroid uptake of I 131 was measured through a specially constructed gamma counting tube. All other counts were made through an Amperex Beta

Bank of America-Giannini Foundation Fellow in Urology.

Read at annual meeting, American Urological Association, Atlantic City, N. J., June 25, 1952.

*Note by editor.* Dr. Rosenberg's manuscript was awarded first prize in the essay competition sponsored each year by the American Urological Association under the Committee on Scientific Research, Dr. Miley B. Wesson, chairman.

<sup>1</sup> Hanzlik, P. J.: Quantitative studies on the gastro-intestinal absorption of drugs: II. The absorption of sodium iodide. *J. Pharmacology*, 3: 387-421, 1912.

<sup>2</sup> Sollmann, T.: *A Manual of Pharmacology*, ed. 7. Philadelphia: W. B. Saunders Co., 1948, p. 817.

Counter, Type 1000. Metal cups containing 3 milliliters of wet samples with calculated infinite thickness for each isotope were used. All samples were calibrated against standards made up from the isotope being used. Total circulating blood volume was calculated on the basis of body weight according to Bonnycastle and Cleghorn.<sup>3</sup>

The animals were prepared by inserting a rectal tube and emptying the bowel. The femoral or jugular vein was exposed so that blood could be sampled quickly. All blood samples were oxalated. In the control animals, an indwelling urethral catheter was inserted. Control samples of blood, urine and stool were obtained. For I 131, background counts were taken from the thyroid. The tracer substance was then mixed with 20 ml. of distilled water and inserted through a 14F catheter which extended 5 cm. inside the rectal sphincter. The catheter was removed immediately and leakage did not occur. The technique of instillation was tested with diodrast and x-ray in two animals and dye was not pushed beyond the confines of the sigmoid colon. Counting with an electric second counter was begun at the beginning of the instillation. For thyroid uptake of I 131, continuous gamma counts were made for at least 10,000 seconds. Blood samples were drawn at 100 seconds after instillation, 300 seconds, 500 seconds and then every 15 minutes for the first 2 hours, every 30 minutes for the next 2 hours, every 2 hours for the fourth to twelfth hour, every 4 hours for the next 12 hours and every 8 hours until the blood level showed a distinct downward curve. The animals were returned to their metabolic study cages 3 hours after insertion of the isotopes. Urine samples were collected continuously throughout the first 3 hours in 3 milliliter amounts. After 3 hours, the catheter was removed and all voidings were measured for beta radiation. Stool specimens were dried, mixed and sampled at 24 hour intervals. Rectal leakage did not occur for at least 3 hours in any case.

For I 131 and P 32, four normal animals and four with transplanted ureters were used for each isotope. For I 131, the thyroid uptake was measured in the entire group of animals. Two normal and two experimental animals were used for Na 24. In all experiments, the average curve of isotope levels for each group of animals (normal and those with anastomosis) fell within 25 per cent of the curve for each animal within the group. In addition, experiments using carrier solutions of iodine, phosphorus and urine were carried out.

*Radioactive iodine studies.*—For I 131, one millicurie of the isotope was instilled. Figure 1, A represents the total circulating microcuries of I 131 in each group of animals. Initial absorption in the normal group at 100 seconds after instillation was five microcuries while in the transplanted group it averaged 18 microcuries. The peak level for the controls, 29 microcuries, was reached in 2 hours and then fell rapidly. For the dogs with uretersigmoidostomy, the peak level at 2 hours was 120 microcuries, a fourfold increase over the normal group. This level was maintained for 8 hours, was still high at 24 hours and then gradually dropped. At 96 hours, in the normal group, the I 131 was barely demonstrable while in the other group there was still ten microcuries in the blood. Radio-

<sup>3</sup> Bonnycastle, D. D. and Cleghorn, R. A.: A study of the blood volume of a group of untrained normal dogs. *Am. J. Physiol.*, **137**: 380-383, 1942.

activity was demonstrable in the urine of normal dogs within 1000 seconds after instillation and urinary excretion of the isotope is represented graphically in figure 1, *B*. Almost all of the isotope placed in the rectum was absorbed and less than 10 per cent was recoverable in the stool in normal dogs (fig. 2, *A*). For the animals with anastomosis, stools contained both feces and urine. Total output of I 131 in these animals averaged only 180 microcuries in 24 hours and a total of 240 microcuries in 48 hours. In normal animals, the average combined

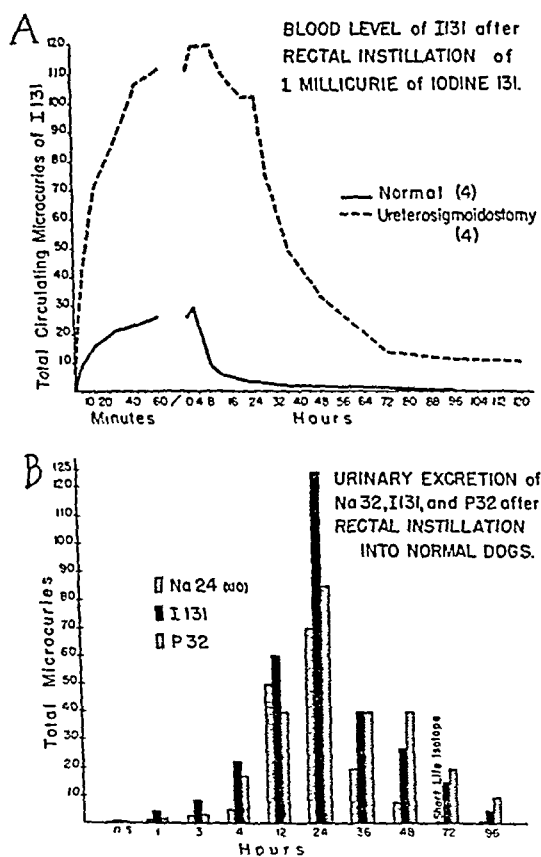


FIG. 1

urinary and fecal excretion was 274 microcuries in 24 hours and 356 microcuries in 48 hours. The average thyroid uptake of I 131 for each group of animals is shown in figure 2, *B*. These values are the actual gamma counts per second made by the counting tube placed over the right lobe of the thyroid. The experimental group had an average circulating blood volume of 32 per cent more than the controls. Hence, if the counts could be validly corrected for actual weight of the thyroid and for blood volume, the rate of isotope absorption in the group with anastomosis would undoubtedly be even higher than is indicated in figure 2, *B*.

In order to determine whether the levels of isotope in the blood represented actual absorption or whether they represented simple ion exchange, a carrier of stock iodine was used in an additional two normal dogs. One millicurie of I 131 was placed into 20 ml. of urine containing 0.8 per cent sodium iodide so that the mixture was hypertonic. This was instilled and except for a slight initial delay, absorption was not inhibited.

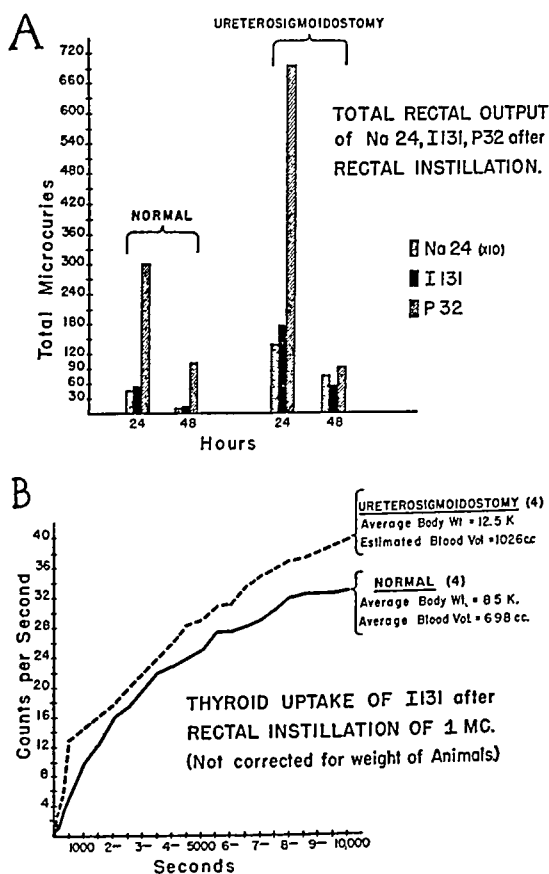


Fig. 2

*Radioactive phosphorus studies.*—One millicurie of isotope was administered rectally. Much of this ion is bound to calcium, magnesium and other organic compounds in feces, and the phosphate content of normal adult feces represents 43 per cent of the excretion of this substance.<sup>4</sup> In the normal animals, an average of 400 microcuries was recovered in the stool and only 600 microcuries was absorbed. With this isotope, as with I 131 and Na 24, radioactivity was demonstrable in the blood within 100 seconds and in the urine within 1000 seconds. Blood levels are shown in figure 3, A. The peak level of 12 microcuries was reached in 4 hours in the normal group. The concentration of the isotope in the

<sup>4</sup> Shohl, A. T.: Mineral Metabolism. New York: Reinhold Publish. Corp., 1939, p. 336.

blood decreased gradually after 8 hours and could still be detected at 96 hours. With the other group, only infinitesimal amounts of isotope were absorbed and blood levels were less than one microcurie at any time.

Additional experiments were then conducted to determine which factors were responsible for inhibiting absorption of phosphate in these animals. Urine contains much phosphate ion and electrolyte competition in the bowel of the ex-

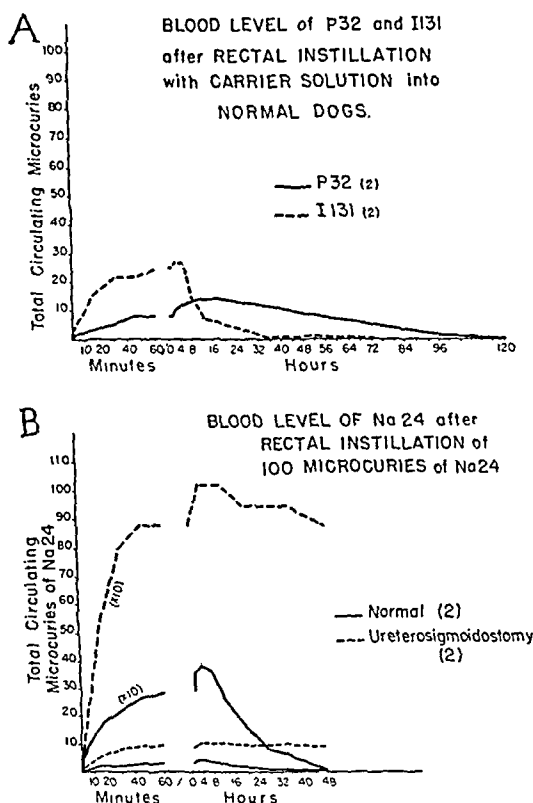


FIG. 3

perimental animals could prevent isotope absorption. Urinary phosphate excretion for 24 hours in two normal dogs weighing 9 kilograms each and on a regular diet was found to average 700 mg. Accordingly, a carrier solution was prepared in which 700 mg. of phosphate (as sodium dihydrogen phosphate) was dissolved in 20 ml. of water, and pH was adjusted to 6.0 with sodium bicarbonate. This was instilled into each of two normal dogs and the curve was approximately the same as that in the control group so that interference with absorption on the basis of ion exchange was not a factor. To determine the effect of urine itself upon the absorption of phosphate, one millicurie of P 32 in 20 ml. of dog urine was instilled into each of two normal dogs. Phosphate absorption was inhibited to the same extent as in the dogs with anastomosis. In the latter,



80 per cent of the administered dose was recoverable in the stool (fig. 2, A). Urinary excretion in normal dogs is shown in figure 1, B.

*Radioactive sodium studies.*—The results of Na 24 absorption are shown in figure 3, B. The blood levels closely paralleled those found with I 131. Na 24 emits more beta radiation than do I 131 and P 32 since it has a much shorter half-life. The dose given was thus only 100 microcuries, or one-tenth of the dose used with the other isotopes. Calculations are based on actual counts, but for comparison, these counts were multiplied by a factor of ten. Urinary excretion was relatively slow as compared with I 131 although beta activity was found in the urine within 1000 seconds after instillation (fig. 1, B). Rectal output of the

TABLE 1. *Blood electrolyte pattern of animals with bilateral ureterosigmoidostomy during isotope experiments*

| DOG                       | UREA                       | CREATININE | PHOSPHORUS                        | CHLORIDE | CO <sub>2</sub> COMB. POWER | SODIUM | POTASSIUM |
|---------------------------|----------------------------|------------|-----------------------------------|----------|-----------------------------|--------|-----------|
|                           | <i>milligrams per cent</i> |            | <i>milliequivalents per liter</i> |          |                             |        |           |
| 1                         | 130                        | 1.4        | 3.9                               | 113.4    | 12                          | 139    | 4.0       |
| 2                         | 54                         | 1.0        | 4.7                               | 110.2    | 20                          | 142    | 4.1       |
| 3                         | 160                        | 1.2        | 4.0                               | 119.5    | 14                          | 147    | 4.2       |
| 4                         | 30                         | 0.8        | 4.5                               | 100      | 26                          | 145    | 4.5       |
| Before surgery            |                            |            |                                   |          |                             |        |           |
| 4                         | 49                         | 0.9        | 4.2                               | 96.4     | 26                          | 140    | 4.7       |
| Two months after surgery  |                            |            |                                   |          |                             |        |           |
| 4                         | 61                         | 0.8        | 4.1                               | 110.5    | 20                          | —      | —         |
| Five months after surgery |                            |            |                                   |          |                             |        |           |

drug is shown in figure 2, A. As with I 131, most of the isotope was absorbed and less than 10 per cent could be recovered from the stools of the normal animals.

*Effect of acidosis on absorption.*—It is of particular interest to know whether there is any difference in absorption in an experimental animal with normal electrolyte balance and one with hyperchloremic acidosis. Observations were therefore carried out on dog 4 (table 1). Preoperatively, absorption curves for I 131 and P 32 were normal. Two months after operation, no electrolyte imbalance had occurred and rectal instillation of I 131 and P 32 was again carried out. Five months after operation, hyperchloremia was present and at this time, sigmoidal absorption studies of I 131 and Na 24 were carried out. No significant difference could be found in the absorption curves in either the balance or the acidotic phase. The curve for I 131 on both trials fell within the average range for all animals with transplanted ureters. That for Na 24 in the acidotic phase and for P 32 in the balance phase also agreed with the curves for the other experimental animals. The absorption of electrolytes by the bowel thus appears to be the same whether or not acidosis is present.

#### MEASUREMENT OF URINARY CONSTITUENTS IN VENOUS BLOOD

*Methods.*—Phase two of the experiment was carried out in two normal dogs and in two experimental dogs. Heparin-coated syringes were used to collect the

blood from the jugular vein, the sigmoid veins and the portal vein, laparotomy being performed to obtain samples. The portal vein was included so that pre-hepatic mixing could be observed. Measurements of the blood ammonia, plasma chloride, blood urea and the pH were carried out on each of the samples. The blood ammonia was determined by the micro-titration method of Barnett<sup>5</sup>; plasma chloride by the method of Schales and Schales<sup>6</sup> and the blood urea by standard laboratory technique using urease and Nessler's reagent. The blood pH was measured with the Cambridge Electron-Ray pH Meter.<sup>7</sup>

*Blood ammonia.*—Table 2 shows the amount of blood ammonia in this series. In both control animals, peripheral (jugular) and portal blood contained nor-

TABLE 2. Blood ammonia in milliequivalents per liter

| DOG               | JUGULAR VEIN | PORTAL VEIN | SIGMOID VEIN |
|-------------------|--------------|-------------|--------------|
| Normal 1.....     | 0.20         | 0.20        | 0.65         |
| Normal 2.....     | 0.21         | 0.27        | 0.90         |
| Transplant 1..... | 0.54         | 0.64        | 6.10         |
| Transplant 2..... | 0.49         | —           | 5.01         |

TABLE 3. Plasma chloride in milliequivalents per liter

| DOG               | JUGULAR VEIN | PORTAL VEIN | SIGMOID VEIN |
|-------------------|--------------|-------------|--------------|
| Normal 1.....     | 103.6        | 102.7       | 103.5        |
| Normal 2.....     | 98.6         | 98.3        | 97.8         |
| Transplant 1..... | 127.6        | 130.2       | 135.5        |
| Transplant 2..... | 117.3        | —           | 121.4        |

mal amounts while blood from the sigmoid vein contained a little more. This increase may be due to absorption of ammonia derived from bacterial decomposition of urea in the large intestine.<sup>8</sup> In the experimental animals the ammonia content of peripheral and portal blood was also slightly higher than in the controls and of signal importance is the high concentration of ammonia in sigmoid venous blood—more than ten times that in the peripheral blood. The increase of jugular ammonia may have occurred because the pre-hepatic ammonia was so increased that the liver could not cope with the load and could not convert it all to urea.<sup>9</sup>

*Plasma chloride.*—The plasma chloride determinations are presented in table 3. In the normal animals, blood from peripheral, portal and sigmoid veins contained essentially the same amount of chloride. However, in the experimental animals, there is increased concentration of chloride in sigmoid venous blood over that in peripheral and portal blood.

<sup>5</sup> Barnett, G. D.: The micro-titration of ammonia with some observations on normal human blood. *J. Biol. Chem.*, 29: 459-462, 1917.

<sup>6</sup> Schales, O. and Schales, S. S.: A simple and accurate method for the determination of chloride in biological fluids. *J. Biol. Chem.*, 140: 879-884, 1941.

<sup>7</sup> Comroe, J. H., Jr.: Methods in Medical Research, vol. 2. Chicago: Year Book Publishers, 1950, p. 179.

<sup>8</sup> Barnett, G. D. and Addis, T.: Urea as a source of blood ammonia. *J. Biol. Chem.*, 30: 41-46, 1917.

<sup>9</sup> Shib, H. E.: The mechanism of increase of blood ammonia concentration. *J. Urol.*, 35: 82-85, 1936.

*Blood urea.*—In this instance, as with the plasma chloride, there was no difference in the normal animals (table 4). The concentration of urea in animals with transplanted ureters was greater in the sigmoid than in the peripheral blood.

*Blood pH.*—It is possible that more acid than alkaline salts are absorbed by the sigmoid because the solution poured into the colon is acid and more anions are available. Accordingly, the actual pH of blood from the peripheral, portal and sigmoid veins was measured (table 5). The pH values of all the samples of blood from the normal dogs were essentially the same. However, the pH of sigmoid blood in the experimental dogs was significantly lower than that of peripheral blood, representing an increase of acid salts in the material being absorbed.

TABLE 4. *Blood urea in milligrams per cent*

| DOG               | JUGULAR VEIN | SIGMOID VEIN |
|-------------------|--------------|--------------|
| Normal 1.....     | 29           | 29           |
| Normal 2.....     | 33           | 34           |
| Transplant 1..... | 120          | 141          |
| Transplant 2..... | 113          | 137          |

TABLE 5. *pH of venous blood*

| DOG               | JUGULAR | PORTAL | SIGMOID |
|-------------------|---------|--------|---------|
| Normal 1.....     | 7.26    | 7.26   | 7.27    |
| Normal 2.....     | 7.28    | 7.27   | 7.28    |
| Transplant 1..... | 7.21    | 7.16   | 7.13    |
| Transplant 2..... | 7.21    | —      | 7.14    |

## DISCUSSION

Urinary electrolytes are absorbed from the sigmoid in a definite manner. Sodium and chloride are absorbed almost entirely and at a similar rate so that, dose for dose, there appears to be no selective absorption of chloride without sodium. In normal animals, phosphorus is absorbed to the extent of 60 per cent of the dose given. However, urinary phosphate presented to the sigmoidal mucosa is bound in some manner to cations in the urine and is not absorbed. The concentration of serum phosphorus in patients with hyperchloremic acidosis is usually normal and occasionally low. Absorption of electrolytes from the bowel is the same in an animal with ureterosigmoidostomy whether or not acidosis is present.

The pH of blood in the sigmoid vein is significantly lower than that of peripheral blood, indicating an excess of acid salts. Since sodium and chloride are absorbed equally well, the amount of chloride absorbed is relatively excessive because the urine which enters the colon contains an excess of acid salts. Acidosis is compensated by the urinary excretion of increased amounts of ammonia and titratable acid so that a vicious cycle is set up and the sigmoid is presented

with more and more acid salts (ammonium chloride, etc.) for reabsorption. In fact, Sartorius and his co-workers<sup>10</sup> have demonstrated that in chloride acidosis produced by the ingestion of large doses of ammonium chloride, repair of the electrolyte imbalance occurred by the renal tubular excretion of increased quantities of ammonia and increased titratable acid with the proportion decrease in loss of fixed base. The fixed base (sodium, potassium, etc.) is absorbed and ferries an equal amount of acid (chloride, etc.) across the sigmoidal mucosa. The remaining chloride in the urine is transported across as the ammonium salt. The abundance of ammonia is produced from two sources—the renal tubule (distal) and the bacterial decomposition of urea in the large bowel. These conclusions are substantiated by the finding of excess ammonia, chloride and urea in blood coming directly from the sigmoid. This evidence of absorption of urea (but not creatinine) by the bowel confirms the work of Bollman and Mann<sup>11</sup> and other workers. Although the molecule of creatinine is larger than the molecule of urea, the reason why it is not absorbed is not clear.

Thus, the electrolyte pattern in hyperchloremic acidosis is consistent. The amount of chloride is excessive, and since this is the principle anion in plasma, acidosis develops. To combat this increase in fixed acid, the bicarbonate-bound base (alkali reserve) is released by the respiratory excretion of carbonic acid so that the carbon dioxide combining power, a measure of the alkali reserve, is decreased. The serum phosphorus remains normal since little phosphorus is absorbed; most of it is excreted in the cloacal content.

The serum potassium is normal in most cases, but in acute episodes of acidosis, severe hypokaliemia may develop. Potassium is freely absorbable per rectum,<sup>12</sup> so that it may be absorbed from the sigmoid and bind chloride in the same manner that sodium does. Most of the potassium is intracellular and only 4.0 to 5.4 milliequivalents per liter are found in the extracellular fluid. Hence a relatively small amount in comparison to sodium is poured into the colon. Patients with severe hyperchloremic acidosis have anorexia, vomiting, polyuria and diarrhea. Hence, potassium intake is diminished and loss from the gastrointestinal tract is increased. In addition, the renal tubular mechanism in severe acidosis and in dehydration<sup>13</sup> is such that excess excretion of potassium occurs to ferry fixed acid in the urine while sodium is conserved by the kidney.

The serum sulfate is moderately elevated in these patients.<sup>14</sup> Absorption of this anion as the salt of fixed base or ammonia undoubtedly accounts for its increase since it returns to normal after rectal tube drainage.

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<sup>10</sup> Sartorius, O. W., Roemmelt, J. C. and Pitts, R. F.: The renal regulation of acid-base balance in man. IV. The nature of the renal compensations in ammonium chloride acidosis. *J. Clin. Investigation*, 28: 423-439, 1949.

<sup>11</sup> Bollman, J. L. and Mann, F. C.: Nitrogenous constituents of blood following transplantation of ureters into different levels of intestine. *Proc. Soc. Exper. Biol. & Med.*, 24: 923-924, 1927.

<sup>12</sup> Hoffman, W. S.: Clinical physiology of potassium. *J. A. M. A.*, 144: 1157-1161, 1950.

<sup>13</sup> Bradley, S. E., Bradley, G. P., Tyson, C. J., Curry, J. J. and Blake, W. D.: Renal function in renal diseases. *Am. J. Med.*, 9: 766-798, 1950.

<sup>14</sup> Ferris, D. O. and Odel, H. M.: Electrolyte pattern of the blood after bilateral uretero-sigmoidostomy. *J. A. M. A.*, 142: 634-641, 1950.

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drome suggests itself. Ureterosigmoidostomy frequently predisposes to chronic pyelonephritis with or without hydronephrosis. Since the serum creatinine is most often normal in these patients, indicating no widespread glomerular insufficiency, and since in some patients hyperchloremic acidosis develops without elevation of the blood urea, indicating minimal or no reabsorption from the bowel, renal tubular acidosis has been suggested as an etiologic factor.<sup>15, 16</sup>

In a study of 12 consecutive patients who underwent cystectomy and bilateral uretero-intestinal anastomosis (11 for carcinoma, one for exstrophy) during the past three years with at least 18 months follow-up, hyperchloremic acidosis developed in eight. Onset of the syndrome in 6 cases was within 4 months after operation, usually within the first month. In 2 cases persistent acidosis developed 1 year after operation and the serum creatinine was elevated indicating diffuse renal damage. In addition, these two patients had recurrent attacks of pyelonephritis and were treated with antibiotics. Excretory urograms revealed diminished tubular excretion of dye. Since urea is absorbed from the large bowel while creatinine is not, the level of blood urea is an unreliable indication of glomerular filtration. The serum creatinine remained normal in ten of the patients, indicating good glomerular function. Good concentration of dye during excretory urograms in these 10 patients indicated at least qualitatively good proximal tubular function. Blood urea was elevated in seven of the 8 patients with hyperchloremia and it was also elevated in three of the 4 patients in electrolyte balance.

None of the eight patients with acidosis nor 4 dogs with hyperchloremia presented evidence of renal tubular acidosis. Urine pH was lower than 6.0 in all of 5 patients tested. Samples of urine during water diuresis were obtained by rectal tube in 4 patients and at the time of nephrostomy in 1 case. Studies of the total titratable acid excreted in the urine of patients with hyperchloremia have not yet been completed but there appears to be increased excretion. In 2 dogs, urine was aspirated from the ureters and the pH of both was approximately 5.0. Specific gravity of urine samples obtained by rectal tube was consistently above 1.014 in all patients and dogs. From the studies reported in table 2 it would seem that production of ammonia by the tubules was adequate. The serum alkaline phosphatase was normal in the four patients with acidosis in whom this was measured. The serum phosphorus was normal in all patients and the potassium was low in only 2 patients during acute episodes. None of the "typical" x-ray findings were present. Renal tubular damage following sulfonamide therapy may also be a possible factor in the production of hyperchloremic acidosis<sup>17</sup> but none of the patients had received any of the absorbable sulfonamides.

Other clinical findings in the group of hyperchloremic patients indicate that renal tubular insufficiency was not a major factor in the early production of

<sup>15</sup> Pines, K. L. and Mudge, G. H.: Renal tubular acidosis with osteomalacia. *Am. J. Med.*, 11: 302-311, 1951.

<sup>16</sup> Lapides, J.: Mechanism of electrolyte imbalance following ureterosigmoid transplantation. *Surg., Gynec. & Obst.*, 93: 691-704, 1951.

<sup>17</sup> Greenspan, E. M.: Hyperchloremic acidosis and nephrocalcinosis: The syndrome of pure "lower nephron" insufficiency. *Arch. Int. Med.*, 83: 271-291, 1949.

hyperchloremia. A low chloride dietary intake (approximately 2 gm. daily) and frequent defecation maintained normal electrolyte balance in 6 patients; one required supplementary sodium bicarbonate. Continuous rectal tube drainage improved the electrolyte pattern of all of the patients while on a normal diet. Only one of the patients in whom acidosis developed early presented evidence of acute pyelonephritis and was treated with antibiotics during the attack. None of the other patients who had acidosis within 4 months after operation required antibiotics and all of these patients have remained asymptomatic with a normal blood electrolyte pattern on a nearly normal diet without prolonged supplementary sodium bicarbonate therapy. If the main defect was renal, prolonged improvement should not have followed the relatively short and simple control of exchange of electrolytes in the sigmoid.

The 2 patients in whom persistent acidosis developed after 1 year had definite renal parenchymal damage, most likely due to obstruction and recurrent pyelonephritis. In these cases, the serum creatinine remained consistently elevated and intravenous pyelograms revealed almost no tubular excretion of dye. Electrolyte control in these patients required prolonged courses of antibiotics, very frequent voidings supplemented by rectal tube drainage, strict restriction of chloride intake and permanent (two years) alkali therapy.

It is believed that the primary factor in the production of hyperchloremic acidosis following ureterosigmoidostomy is in most cases reabsorption of urinary constituents, primarily anions, from the large bowel. Since the maintenance of acid-base balance is primarily the function of the kidney, impaired renal function may predispose to the production of acidosis or aggravate it once it has developed. In these cases parenchymal damage is usually widespread so that glomerular insufficiency is also present and the serum creatinine rises progressively. Renal tubular acidosis may be present in a patient with ureterosigmoidostomy, possibly as a result of chronic pyelonephritis. Indeed, in borderline compensated tubular disease, the added burden of reabsorption of acid salts from the sigmoid and chronic pyelonephritis could logically precipitate decompensation with the production of clinical tubular acidosis.

There are many varying factors in certain cases which may explain why acidosis does not develop and why a normal blood urea is maintained in the presence of acidosis. Individual differences in diet and bowel habits may be among them. Alkaline ash, low salt and low protein diets are conducive to a decrease of urinary anions and urea. Frequent defecation is of obvious importance. Although metaplasia of the sigmoid has not been observed, in most patients with reabsorptive acidosis, electrolyte balance is re-established within six months to a year after the operation. This would appear to represent a gradual compensation by the body rather than a decrease in absorption.

#### SUMMARY

Radioactive tracer techniques and analyses of sigmoid venous blood have been used to measure absorption of urinary constituents from the sigmoid. In patients with bilateral ureterosigmoidostomy, electrolytes are continuously re-



absorbed according to a definite pattern and this may be a primary factor in the production of hyperchloremic acidosis. The sigmoidal mucosa per se has no absorptive selectivity for one electrolyte to the exclusion of another. Sodium and chloride are absorbed well; phosphate is inhibited by urine. Potassium and sulfate also appear to be absorbed. The absorptive potential of the bowel remains the same whether or not acidosis is present. Venous blood draining the sigmoid wall contains more ammonia, chloride and urea than does peripheral blood. The pH of sigmoid venous blood is lower than that of peripheral blood.

Urine which empties into the bowel contains more acid than alkaline salts and increased ammonia and titratable acid. Excess anions, particularly chloride, are absorbed as the ammonium salt as well as the salt of fixed base such as sodium and potassium. Urea is absorbed while creatinine is not.

Clinically, although reabsorption appears to be the major etiologic factor in most cases of hyperchloremic acidosis, severe renal insufficiency may predispose to the production of acidosis or may aggravate acidosis once it develops. Renal tubular acidosis may co-exist in a patient with ureterosigmoidostomy.

The author is indebted to Dr. John A. Luetscher, Jr., Dr. Robert R. Newell and Dr. Henry M. Weyrauch for invaluable guidance in carrying out the experiments.

## PRESENT STATUS OF SURGICAL PROCEDURES FOR URETERO-ENTERIC ANASTOMOSIS

A. WAITE BOHNE

*From the Henry Ford Hospital, Detroit, Mich.*

Several years ago when Reed Nesbit was at work on his technique of elliptical anastomosis he remarked that very few ideas were completely original. If carefully perused, the literature would reveal that the main hypothesis had been previously considered. The application or development of the procedure was the only innovation.

Surgical techniques and ideas are developed, tried, and discarded only at a later date, under different conditions, again to be tried with success. This situation exists today when applied to procedures developed for uretero-enteric anastomosis. Hinman and Weyrauch<sup>1</sup> in their comprehensive study in 1936 listed and described some 60 surgical techniques which they classified into eleven surgical principles. Some of these techniques were first proposed in the latter part of the last century, but due to conditions existing at that time many of them were impractical.

The following are the eleven principles as taken from Hinman and Weyrauch:

1. The formation of a fistulous tract.

Simon 1851, Coffey 1930, Kirwin 1930, Ferguson 1931, Higgins 1933, Hinman 1935, Wadhams & Carabba 1933, Brenizer 1935, Farrell 1938, Jewett 1940, Thomson 1949.

2. Direct implantation.

Smith 1878, Chaput 1892, Peterson 1900, Beaver & Mann 1932, Nesbit 1948, Cordonnier 1949.

3. The formation of a muscular channel from the wall of the intestine.

Bardenheuer 1886, Depage and Mayer 1904, Tichoff 1905, Stiles 1907, Jefferson 1918.

4. The preservation of the ureteral orifice.

Maydl 1892, Bergenhem 1894, Jaja 1901, Peterson 1900, Moynihan 1905, Beck 1906, Goodwin 1951.

5. Temporary diversion of the urine.

Giordano 1892, Peters 1899, Heitz-Boyer 1912, Coffey 1925, Hinman 1926, Ferguson 1931, Hinman 1935, Vose 1945, Melick 1949.

6. The formation of a valve from an internal flap of the intestinal wall.

Vignoni 1895, Fowler 1896, Pisani 1896, Davalos 1945.

7. The use of mechanical devices.

Boari 1895, Chalot 1896, Evans 1899, Zollinger 1934, Stevens 1943.

8. Insertion into a natural duct.

Read at annual meeting, North Central Section American Urological Association, Minneapolis, Minn. October 10, 1952.

<sup>1</sup> Hinman, Frank and Weyrauch, H. M.: Internatl. Abstract of Surgery, 64: 313-363, 1937.

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<sup>1</sup>Hinman, Frank and Weyrauch, H. M.: Internatl. Abstract of Surgery, 64: 313-363, 1937.

Roux 1900, Eaton 1910, Baird 1917,<sup>2</sup> Dardel 1922, Kehl 1923.

9. The submucosal principle.

Krynski 1896, Coffey 1910, Coffey 1925, Turness 1928, Mayo 1930, Higgins 1933, Hinman 1935, Foley 1936, Schinagel 1948, Leadbetter 1951.

10. Colostomy for temporary diversion of the fecal stream.

Barber 1915, Higgins 1931, Nesbit 1933.

11. The use of the intact ureter.

Ferguson 1931, Winsbury White 1933, Higgins 1933, Poth 1935, Nesbit 1935, Brenizer 1935, Palmer 1936, Flocks 1947.

As Hinman states, "The historical material is of importance to the surgeon of today only insofar as it teaches the way to implant ureters more successfully than has been done in the past." Since the eleven principles still apply today and recent techniques fall into one or more of these categories, it seems worthwhile to reiterate these principles. The liberty has been taken to add some of the more recent contributors in what seems to be the appropriate place. The additions are not meant to be all inclusive and many omissions are certain. Some investigators have made small changes in operative technique; others have devised special instruments to facilitate the operation or to eliminate some of the hazards. Others have combined the good points of several techniques to accomplish the same purpose.

From the foregoing list, as Hinman states, "It would seem that every surgical principle imaginable has been tried." The old adage certainly applies that where there exist many ways to perform a surgical procedure, the perfect way has not yet been found.

By scanning the eleven principles it can be seen that all were developed to overcome one or more of three basic hazards: Leakage at the site of anastomosis; obstruction of the urinary tract; and infection of the urinary tract.

In many instances a procedure has been developed to obviate one specific danger. Some techniques combine two or more of the principles to insure greater safety. None of the eleven methods in itself successfully overcomes all the disadvantages.

Keeping the above hazards in mind, brief consideration is now given to the previously enumerated principles. The formation of a fistulous tract, whether by cautery or necrosing suture, eliminates neither infection nor obstruction. All fistulous tracts have a tendency to close. This usually occurs by cicatricial contracture or by mucosal overgrowth. Obstruction of the urinary tract follows naturally.

Since the establishment of the fistula is by means of necrosis, devitalized or necrotic cells provide ample opportunity for infection to occur and spread. The hoped for seal of the two opposing mucosal surfaces also may be incomplete. When this occurs, extravasation of urine into the bowel wall gives rise to obstruction and infection. Riba<sup>3</sup> in his experimental work in 1939 showed that fistulous openings no matter how made did not function well.

The only advantage of this method appears to be its combination with another principle, the submucous tunnel, which reduces the possibility of leakage.

<sup>2</sup> Baird, J. S., Scott, R. L. and Spencer, R. D.: *Surg., Gynec. & Obst.*, 24: 482-484, 1917.

<sup>3</sup> Riba, L. W.: *J. Urol.*, 42: 27-34, 1939.

The direct implantation of the ureter has both advantages and disadvantages. The direct application of mucosa to mucosa provides adequate, immediate unobstructed drainage of urine. This is especially true when the elliptical anastomosis is used since the ostium is 3.1416 times the diameter of the ureter. Fort and Harlin<sup>5</sup> in comparing techniques found the average output of urine the first 24 hours to be directly proportional to the length of the tunnel. In a long tunnel the amount was 370 cc, in a short tunnel 1180 and in a direct anastomosis 2100 cc. Infection at the site of union is not so great as in the fistulous tract since no devitalization of tissues occurs. Later ascending infection may be more likely, however, since reflux of gas and/or fecal material has been observed.

Leakage at the site of union is more likely to occur in this type since there is no protective tunnel sealing the junction. This disadvantage, however, is purely one of technique, for as Hinman states, "When sutures are placed properly leakage does not occur."

The muscular channel from the wall of the intestine has not proven successful. Originally it was designed to prevent leakage and facilitate drainage, but fails in these aspects. An efficient seal is provided only if the opposing serosal surfaces are sufficiently scarified, since normal serosa does not adhere to normal serosa. Some inflammatory or traumatic destruction of the serosa must occur. If an efficient seal is created, the subsequent scarring contracture then produces obstruction which leads to dilatation and enhances the preexisting infection. The so-called "stripping action" of the bowel musculature has not been shown to be of any value in aiding peristaltic drainage of the ureter.

Preservation of the ureteral orifice is not practicable in most cases of carcinoma of the bladder. In exstrophy and other conditions in males it may provide a satisfactory anastomosis. In females the pelvic organs may have to be removed. It does not prevent infection as might be assumed because the valve-like action of the intramural portion is not always competent and reflux may occur.

Lymphatic drainage also allows the infection to be carried up the ureter. Obstruction should be lessened, however, as in the direct method.

Temporary diversion of the urine by means of catheters provides early adequate drainage of urine in most cases. Obstruction by plugging of the catheters with debris, however, may occur and damage to the ureteral wall due to pressure of too large a tube may lead to later complications. Infection is more likely since any foreign body in the urinary tract enhances the process. Valve formation from an internal flap of intestinal wall has been proposed to prevent reflux of fecal contents into the ureteral canal. Frequently the flap has become necrotic and sloughed or has again become adherent and produced obstruction. Protection against leakage is difficult to obtain and if insured usually results in contraction and subsequent obstruction.

Mechanical devices of all types have been unsatisfactory. The copper tubes of Chalot or later the vitallium tubes of Stevens<sup>4</sup> have soon become plugged with calcific material. Even the modern day use of plastics has not completely eliminated this difficulty, as they too may become plugged. All other devices

<sup>4</sup> Stevens, A. R. and Lord, J. W.: *J. Urol.*, 50: 574, 1943.

such as "buttons" or dress snaps give rise to the same difficulties as in the principle of the fistulous tract.

Insertion into a natural duct has been mainly experimental. In man the only natural duct in the lower intestinal tract is the appendix. In many individuals it has been removed. In some it will be found to be stenosed and unsuitable. If intact and suitable for use it provides drainage for only one kidney unless concomitant uretero-ureteral anastomosis is performed. This secondary procedure only tends to enhance the risk.

The submucosal principle has been considered by many as the preferred method of anastomosis. Its chief advantage is the complete seal afforded by the

#### Influence of Phosphate Ion on Chloride Absorption.

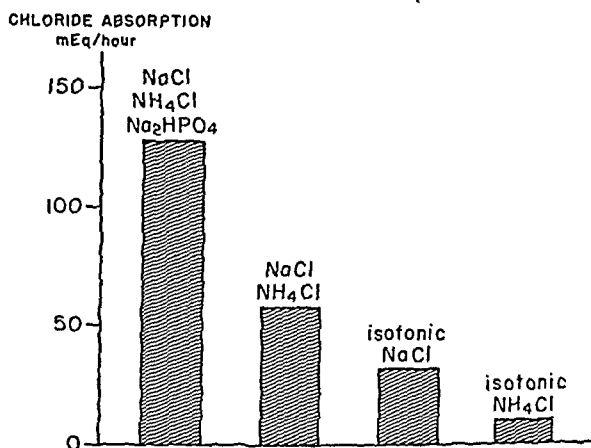


Fig. 1

trough or tunnel thus preventing leakage. As Vermooten<sup>5</sup> states, "The chief advantage of the submucous method of transplantation is the prevention of peritonitis from a leak at the site of the transplantation and not as has been supposed the formation of a valve". The tunnel principle was designed to provide a valve similar to that of the intermural portion of the ureter, thus inhibiting reflux and ascending infection. It has provided some protection against reflux as shown by Higgins<sup>6</sup> but infection and obstruction are prone to occur.

Dean<sup>7</sup> reported 72 per cent of Coffey 1 type transplants showed grade one to two dilatation two weeks postoperatively. Fort and Harlin<sup>8</sup> concluded that "There is a direct ratio between the degree of dilatation of the ureters, pelves and calyces and the length of the submucous tunnel. The same ratio holds true with regards to ascending infection both early and late". Aberhart<sup>9</sup> states that in approximately 75 per cent of his cases hydro-ureter and hydronephrosis occur early and once established are constant and progressive.

<sup>5</sup> Vermooten, Vincent: J. Urol., 32: 273-277, 1934.

<sup>6</sup> Higgins, C.: J. Urol., 37: 90-105, 1937.

<sup>7</sup> Dean, A. L.: J. Urol., 63: 858-862, 1950.

<sup>8</sup> Fort, C. A. and Harlin, H. C.: J. Urol., 65: 1006-1012, 1951.

<sup>9</sup> Aberhart, Carl: N. Y. State J. Med., 49: 2933-37, 1949.

Colostomy for temporary diversion of the fecal stream was advocated mainly to eliminate the hazard of infection. At that time there were no satisfactory antibacterial agents suitable for instillation in the intestinal tract or by oral medication for lower sterilization. Therefore the temporary diversion was only partially successful in eliminating this hazard. Since colostomy may be used with any method of implantation the hazards of obstruction and leakage cannot be considered. The use of the intact ureter on the whole has the same disadvantages as the submucosal principle since all of these employed the submucous trough as a preliminary part of the procedure.

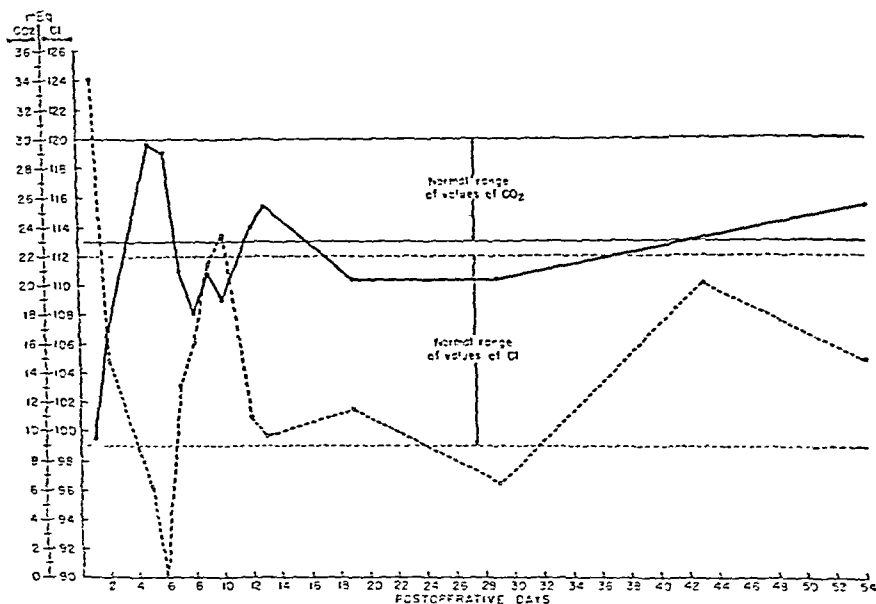


FIG. 2

The foregoing evaluation has been based mainly on the three basic hazards: infection, obstruction and leakage. To these must now be added a fourth, common to all types of uretero-enteric anastomosis and prevented by none. This hazard is the electrolyte imbalance that so frequently follows transplantation. Ferris and Odel<sup>10</sup> in 1950 reviewed 112 cases with the finding that 79 per cent manifested some degree of hyperchloremia and 80 per cent manifested some degree of acidosis. While the exact nature of this mechanism has not been definitely established, reabsorption from the intestinal tract seems to be the major factor.

Lapides<sup>11</sup> believes that renal tubular damage is necessary to incite the onset. Rosenberg<sup>12</sup> recently showed that no selectivity existed for sodium, chloride, potassium or sulfate and that phosphate reabsorption was inhibited presumably by the urine. Rupe and Bohne<sup>13</sup> have demonstrated that the presence of phos-

<sup>10</sup> Ferris, D. O. and Odel, H. M.: *J. A. M. A.*, 142: 631-641, 1950.

<sup>11</sup> Lapides, Jack: *Surg., Gynec. & Obst.*, 93: 691-704, 1951.

<sup>12</sup> Rosenberg, M. L.: *In press, J. Urol.*

<sup>13</sup> Rupe, C. F. and Bohne, A. Waite: (To be published).



phate ions enhanced the reabsorption of chloride and other ions (fig. 1). While renal damage may be a factor or so-called tubular acidosis occur it only becomes manifest when the renal damage reaches an extreme degree. Reason to doubt the validity of the hypothesis of tubular damage or tubular acidosis is demonstrated by a recent case. A 40-year old woman had ureterosigmoid anastomosis performed for incontinence four years ago. Repeated severe episodes of pyelonephritis ensued until permanent colostomy was established. Acidosis had been severe, persistent and difficult to control. By means of a Marchetti operation bladder continence was established, following which the ureters were removed from the bowel and re-anastomosed to the bladder.

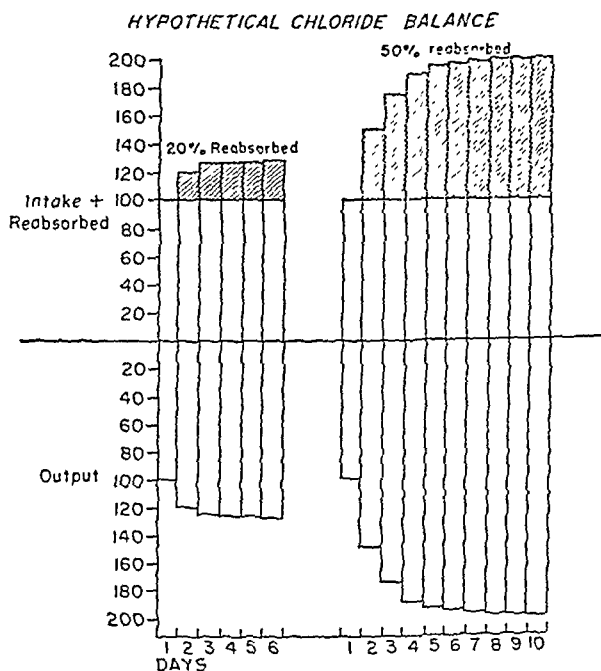


FIG. 3

Figure 2 shows the chloride shift that occurred immediately. While there was adequate reason to believe that moderately severe tubular damage was present the kidneys excreted such an amount of chloride that alkalosis ensued despite efforts to maintain chloride levels by intravenous and oral medication.

Rupe<sup>13</sup> proposed that all reabsorption tends to establish a balance between intake and output (fig. 3). Any inciting factor such as diarrhea, dehydration, infection, renal or systemic, could disturb this balance, thus producing acidosis. While all the exact mechanisms have not been clarified, suffice to say that in most cases hyperchloremia can be controlled by the regimen as outlined by Ferris and Odel.<sup>10</sup> Thus the fourth basic hazard has been to a large extent abolished. What then is the procedure or combination of procedures which will best eliminate the other three basic hazards: infection, obstruction and leakage.

In 1895 Maclair transplanted ureters into the excluded sigmoid. Later

other investigators advocated the same procedure. In 1933 Nesbit<sup>14</sup> wrote, "Colostomy as a preliminary measure before ureteral transplantation is proposed as a method for eliminating this hazard of infection." Higgins<sup>15</sup> in 1933 did permanent colostomy in dogs only to find the lower segment after two years contracted down to no capacity. Bisgard,<sup>16</sup> Rubin,<sup>17</sup> and Thompson<sup>18</sup> reported good results using an isolated sigmoid loop in dogs. Blair<sup>19</sup> in 1916 and Gilchrist and Merricks<sup>20</sup> in 1950 proposed the use of the cecum as a urinary pouch. Two drawbacks attend this procedure however, one the ileocecal valve is not always competent and secondly catheterization of this pouch is necessary, annoying and introduces infection.

Preliminary permanent colostomy would seemingly offer the most effective way to overcome the hazard of infection. A semi-sterile container with sphincteric control is thus created reducing liability of infection at the time of anastomosis and subsequent ascending urinary tract infections, the only disadvantage being the social burden of an inguinal colostomy.

Obstruction of the urinary tract must be eliminated by the actual transplantation technique. Review of the methods would certainly reveal that only the direct method offers such freedom from obstruction.

Leakage at the site of anastomosis remains now to be eliminated. Proper placement of sutures as pointed out by Hinman is essential. Brackin<sup>21</sup> in 1940 and Brunschwig<sup>22</sup> in 1950 recommended leaving a strip of parietal peritoneum attached to the ureter. If this is done rapid sealing of the anastomosis site occurs and practically all danger of leakage is thus eliminated.

#### SUMMARY

The various surgical principles involved in uretero-enteric anastomosis as presented by Hinman and Weyrauch in 1936 have been reiterated and additions made in the light of more recent work in this field. An attempt has been made to evaluate each of these from the standpoint of three basic hazards inherent in the operation: infection, obstruction and leakage.

The fourth hazard of electrolyte imbalance is discussed briefly. A rational composite of techniques is presented comprising preliminary permanent colostomy, direct implantation of ureters into an excluded portion of the recto-sigmoid, and peritoneal strips as an adjunct to prevent leakage at the site of anastomosis.

<sup>14</sup> Nesbit, R. M.: Advanced bladder and urethral tuberculosis: Treatment by ureteral transplantation following preliminary colostomy. *Am. J. Surg.*, 22: 547, 1933.

<sup>15</sup> Higgins, C. C.: Discussion.<sup>17</sup>

<sup>16</sup> Bisgard, J. D. and Kerr, H. H.: *Arch. Surg.*, 59: 588-593, 1949.

<sup>17</sup> Rubin, S. W.: *J. Urol.*, 60: 874-906, 1948.

<sup>18</sup> Thompson, H. T.: *J. Urol.*, 64: 85-101, 1950.

<sup>19</sup> Blair, V. P.: *Surg., Gynec. & Obst.*, 22: 352, 1916.

<sup>20</sup> Gilchrist, R. K., Merricks, J. W., Hamlin, Howard H. and Rieger, I. T.: *Surg., Gynec. & Obst.*, 90: 752-760, 1950.

<sup>21</sup> Brackin, R. E.: *Arch. Surg.*, 40: 658-671, 1940.

<sup>22</sup> Brunschwig, Alexander and Pierce, V. K.: *A. M. A. Arch. Surg.*, 62: 125-28, 1951.

## DELAYED CYSTOGRAMS

CHARLES MONTGOMERY STEWART

*From the Department of Urology, The Moore-White Clinic, Los Angeles, Calif.*

For several decades cystography has provided urologists with permanent visual records of certain diagnostic information which is unobtainable by any other method. Simple variations of the original cystographic technique have improved and broadened the diagnostic application of this procedure. X-ray evidences of variations in size, outline, elasticity, displacement, retention, and the presence or absence of space-occupying lesions of the bladder have usually been obtained by the use of the plain cystogram, the contrast cystogram or the after voiding cystogram. If ureteral reflux was not demonstrated almost immediately with any of those techniques, it was generally assumed that it would not occur. The term "delayed cystogram" accurately describes a diagnostically informative variant of the usual x-ray bladder study.

Early in 1948 an accidental change in our usual cystogram routine proved productive of some interesting and confusing results. Contrast medium had been instilled into the bladder of an adult female suffering from a cystoscopically proved bladder neck contracture. The patient moved during exposure of the immediate film and the technician was advised to repeat the exposure. Approximately 30 minutes elapsed before this was accomplished. This second film was believed to have been underexposed, according to the technician's later explanation, and without having developed either of these two films, she decided a third picture was necessary. The third film was exposed almost 60 minutes after the instillation of the contrast medium. A one hour delayed cystogram had been recorded inadvertently. The first film showed the typical trabeculated outline of a chronically obstructed bladder. Bilateral ureteral reflux was evident on the 30 minute delayed exposure. The 60 minute delayed picture recorded a cystographic silhouette increased in circumference in proportion to the added volume of urine excreted during this interval. It also disclosed a complete disappearance of the bilateral ureteral reflux evident on the 30 minute film. This patient proved most co-operative and immediately became a willing experimental mammal. On several occasions she permitted delayed cystographic films to be taken at 15 to 30 minute intervals for periods as long as 3 hours.

Subsequently this technique has been used on patients in all age groups. The unusual results obtained in some instances can be readily explained; in others, the findings are at wide variance with accepted theories of ureterovesical physiology.

### DEFINITION AND METHODS

When opaque media are instilled into the urinary bladder and retained continuously while x-ray exposures are obtained at variable intervals during the next

Read at annual meeting, American Urological Association, Atlantic City, N. J., June 25, 1952.

Funds for this investigation were furnished by the Moore-White Medical Foundation, Los Angeles, Calif.

one to three hours, the resulting film studies have been termed "delayed cystograms."

Instillation is accomplished per catheter, using a piston syringe. Filling is continued until moderate bladder distention causes the piston to be slowly forced back when thumb pressure against the piston is released. The amount of medium used is variable. One to four ounces usually is a sufficient quantity for infants and children, and four to eight ounces adequate for adults. The instillation should be carried out slowly, preferably using a slightly warmed contrast medium. The bladder should not be distended past a point of comparative comfort.

In female children and in adult females of nervous temperament, a preliminary competent local urethral anesthetic is recommended. This markedly reduces the sensation of urgency resulting from passage of the catheter, as well as the chemical irritation common in some degree to all contrast media.

Of four types of contrast media used, Urokon is believed to cause the least degree of chemical urgency when retained in the bladder for two to three hour intervals. Use of a 15 per cent to 20 per cent concentration of contrast medium is necessary. This concentration is desirable in detection of beginning reflux, especially in those instances where the medium is diluted as it enters a dilated ureter which has a partially incompetent orifice.

Films are exposed immediately following the instillation, and at 15 to 30 minute intervals thereafter. Reflux has been delayed in some instances as long as two and one-half to three hours. Reflux may occur at one interval and disappear at a later interval. For this reason each film should be developed and viewed immediately. The time interval and variations in angle of exposure can then be changed to supplement the immediate x-ray findings.

In infants and in children too young to co-operate, instillation should be made through a 5 cc Foley retention catheter of small caliber. The contrast medium is then retained in the bladder for any desired time interval by a catheter clamp.

#### THEORETICAL CONSIDERATIONS

Conclusive proofs of the cause and effect of vesico-ureteral reflux are still controversial in spite of many years of careful clinical and experimental observations. It is generally accepted that urinary infections, chronic or recurrent; neurogenic defects, congenital or acquired; prenatal structural and functional variations from the normal, and postnatal obstructive uropathies may contribute alone or in variable combinations to the occurrence of ureteral reflux. The great majority of teaching textbooks deny the occurrence of reflux in the normal individual. Prather stated "for reflux to occur it is necessary to have sustained tonus of the bladder musculature as it resists distention, and that the anatomical features of the ureterovesical junction govern the frequency or incidence of vesico-ureteral regurgitation." Graves and Davidoff concluded after extensive experimental animal studies that "reflux depends primarily upon sustained tonus of bladder musculature as it actively resists distention."

Some authors believe that infection must first occur and ureterovesical dysfunction then follows; others state that infection is secondary to disturbed behavior of the bladder and ureter.

The wide divergence of investigative opinions loudly proclaims how imperfectly understood is the neurophysiology of this region. Expansion of ureteral or bladder walls provides the stimuli causing contractions of these organs, according to the findings of Lapides' careful investigations. Talbot and Bunts report the normal autonomous character of ureteral function and its intolerance of over-distention because of lack of central nervous system control. The normal distensible activity of the bladder is controlled by centers in the cord, midbrain and cerebral cortex. This adaptability of the bladder to overdistention is lost when all central nerve control is absent, and it then simulates the normal action of the ureter as it attempts to rid itself of urine in small amounts at frequent intervals. Bunts and Talbot conclude that no direct neurogenic factors were responsible for vesico-ureteral reflux observed in 16 of 331 paraplegic patients studied over a two year period. They concluded, "that reflux probably resulted from distortion and perhaps rigidity of the ureterovesical orifice. Its occurrence appears to be intimately related to cystitis associated with hypertonicity and trabeculation. Pressure alone will not produce reflux in the absence of such distortion, but may enhance its effect." These authors used a delayed 20 minute exposure following instillation of contrast medium. They state that overdistention of the bladder with contrast medium was not necessary,—“if reflux did not appear with 150 cc of medium it did not appear at all.”

Quinby contends that regardless of the cause of ureteral dilatation, peristalsis is impaired early. Greene has written that with wide dilatation, the ureter may become hypertonic, causing functional obstruction.

Several authors agree that structural and functional changes in the upper urinary tract follow inflammations of varying degree. They contend that dilatation may start in the kidney and descend, or the dilatation may have its origin in the ureter and ascend.

#### CYSTOGRAPHIC OBSERVATIONS

Ureteral reflux has been recorded by delayed cystogram in instances when accepted theories dictated reflux was unlikely, and conversely, it could not be demonstrated in other instances when previously accepted theories dictated its occurrence. Does reflux occur normally, or must it result only from an existing or a previous pathological state? Why doesn't reflux always occur in those individuals whose widely patent ureteral orifices appear to have no degree of competence when visualized cystoscopically? How can we explain the reflux through some ureteral orifices which are visually competent when observed cystoscopically? To further agitate our confused physiological concepts of the ureterovesical junction, we obtained cystographic records of patients in whom reflux occurred at one interval unilaterally or bilaterally, and then disappeared unilaterally or bilaterally at a later interval (figs. 1 and 2).

If delayed reflux is demonstrated once in a given individual, should it always recur when the delayed cystogram is repeated? Should it recur only occasionally? There are some individuals in whom we are unable to cause its recurrence a

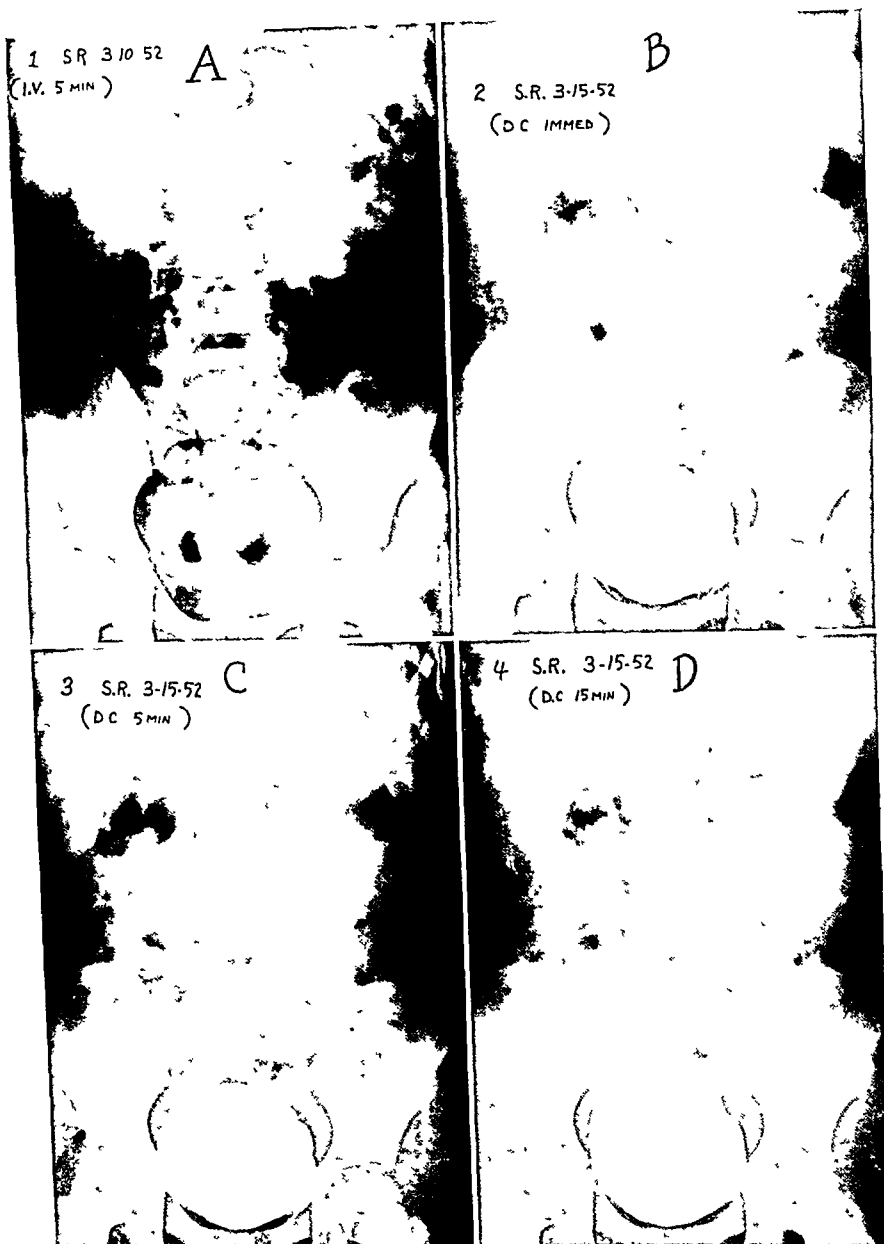


FIG 1 S. R., a girl aged 5 years, complained of recurrent pyuria, fever and chills since birth. Diagnosis, congenital vesical neck obstruction.

A, excretory urogram, 5 minutes. Mild dilatation of left kidney; questionable dilatation on right. B, delayed cystogram, immediate film, beginning reflux, lower right ureter. C, delayed cystogram, 5 minutes; reflux in lower ureter on right has disappeared. D, delayed cystogram, 15 minutes, bilateral reflux evident in kidneys; upper right ureter obvious, lower ureters not outlined.

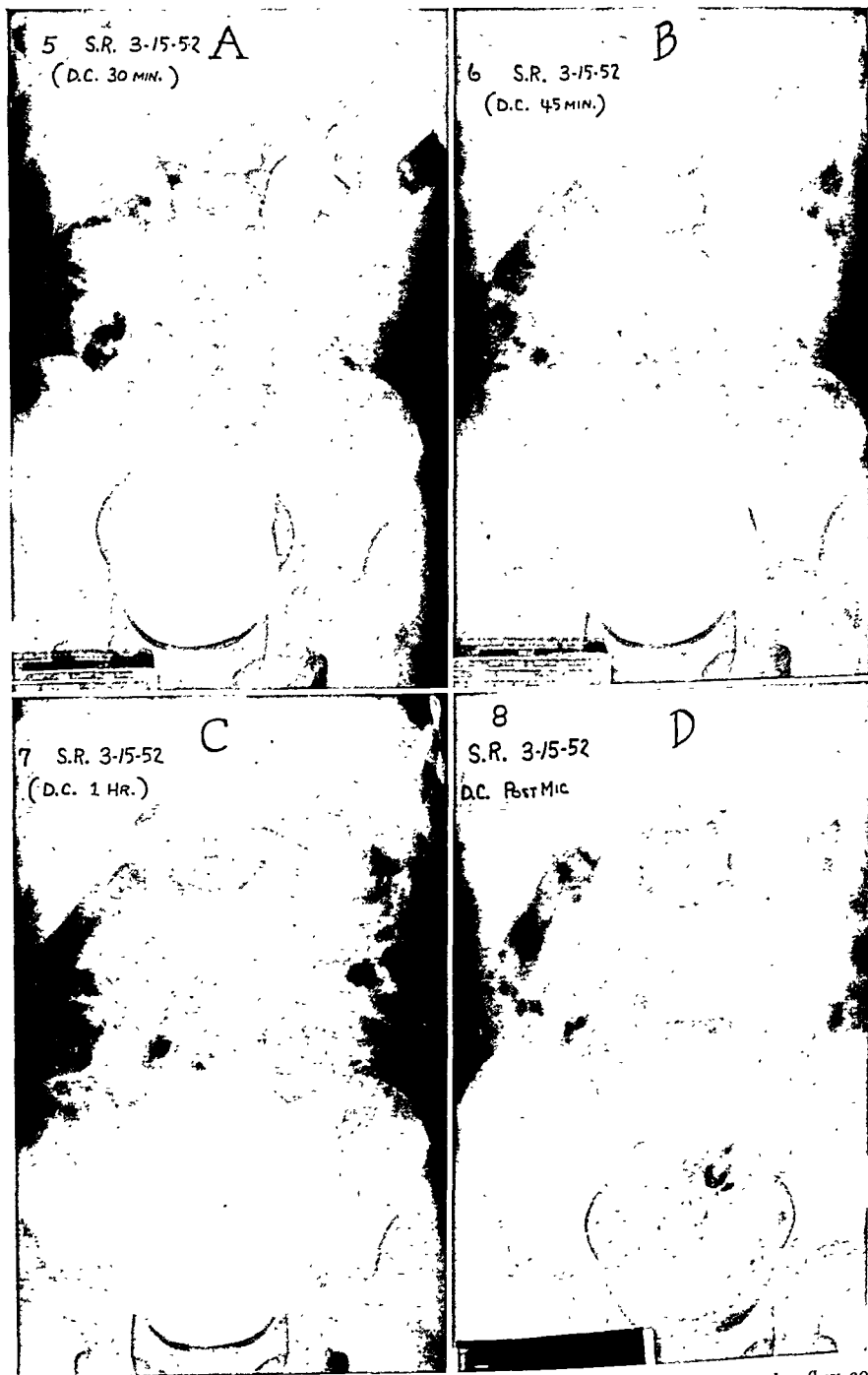


FIG. 2. Same case as figure 1. A, delayed cystogram, 30 minutes; bilateral reflux complete; bilateral renal and ureteral dilatation. B, delayed cystogram, 45 minutes; reflux disappeared on right; only faint outline on left. C, delayed cystogram, 60 minutes, no recurrence of right reflux; questionable faint outline on left. D, delayed cystogram, post-micturition; no recurrence of reflux on right; obvious recurrence of reflux on left; bladder residual and trabeculation obvious.

The patient had ureteral orifices which had a normal appearance of competence when ; and cystoscopically

second time. Is it possible that the function of the ureterovesical junction is capable of this degree of operational variety?

Can an obvious hydronephrosis and hydro-ureter be demonstrated by delayed cystogram in an individual whose excretory urograms and retrograde studies provide perfectly normal pyelographic silhouettes? These findings will be demonstrated in the projection slide demonstrations to follow.

Can delayed reflux occur into an ectopic ureteral opening located in the urethra just proximal to the vesical sphincter? Two cases in which this occurred will be shown during the following projection slide studies.

Film studies of delayed cystograms reveal some variations in uretero-vesical junction performance, which cannot be explained entirely on the basis of our present concepts of the physiology of this region. Is the urinary tract occasionally a physiological nonconformist? Does the ureterovesical junction possess a behavior pattern capable of whimsical aberration? Undoubtedly these simulated vagaries will be explained when the final facts concerning the functional cause and effect mechanisms of the bladder and ureter have been revealed. I have no experimental evidence or plausible theory to support any attempt to explain some of the unusual occurrences shown in the foregoing and following film studies.

The author hopes that this report will stimulate sufficient interest for further investigations. Future clinical study and experimental investigation should provide the answers to the many questions that can be raised concerning the evident variable physiological capabilities of the vesico-ureteral junction.

*511 South Bonnie Brae St., Los Angeles, Calif.*

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## LITHOLAPAXY

REED M. NESBIT

*From the Department of Surgery, University of Michigan Medical School, Ann Arbor, Mich.*

1 Removal of stones from the urinary bladder was among the earliest operations to be performed by our surgical forefathers and today comprises one of the heritages of our own specialty. In the era that developed lithotomy the incidence of vesical calculus must have been great for the first description of the operation by the philosopher Celsus indicates that in his day the operation was performed only on young persons between the ages of nine and fourteen years.

1 The earliest lithotomies were all performed by perineal incision for the suprapubic approach was never found to be sufficiently safe until the listerian era. The various early techniques of perineal lithotomy were anatomically clumsy as well as brutal, and patients in those days must indeed have suffered miserable despair before submitting to the cruel agonies and uncertain results which attended the cutting for stone. And today one can find cause to sympathize with the frequency with which those surgical pioneers must have performed their operations unwittingly for non-calculus diseases which were yet to be discovered.

1 The development of operations that were designed to break or crush stones in the bladder by the use of instruments introduced through the urethra came about in the 19th century. In 1824 Jean Civiale of Paris performed the first successful lithotripsy on a living patient with an instrument that he called a litholabe. This consisted of two straight metal sheaths, one fitting inside the other, the inner of which terminated in three curved spreading arms which closed by retraction of the inner into the outer sheath, engaging the stone. Then an iron rod with a screw tip was passed down through the instrument and bored and crushed the calculus. Following fragmentation an attempt was made to wash out the debris through a catheter. This device had definite limitations of usefulness and eventually gave way to more efficient instruments.

The prototype of the modern lithotrite was designed by Huerteloup in 1832. This instrument had two blades, one riding upon the other which grasped and held the stone and the crushing force was applied by a hammer at the end of the movable male blade. Later a screw handle was developed which permitted compression of the lithotrite jaws. The early instruments were fragile and often broke during operation endangering the patient; and it soon became evident that crushing the stone often did not cure the patient. In fact, many actually suffered more after lithotripsy than before as the result of fragments left in the bladder. Civiale had advised the removal of these fragments and had attempted to do so by using a catheter to wash them out after operation, but many of his contemporaries relied upon nature to evacuate the pieces. Eventually an evacuating device was made which consisted of a curved metal catheter with a rubber bulb attached but this was not efficient so lithotripsy in Europe did not enjoy a general acceptance.

Presidential address, North Central Section, American Urological Association, Minneapolis, October 10, 1952.

The operation was not placed upon a sound and reliable basis until Bigelow corrected the major defects inherent in the earlier procedures. This ingenious Bostonian did not create any new instruments; he simply improved upon the old and also defined and asserted the principles of safe and successful lithotripsy. His contributions to the operation were these:

He improved the design of the lithotrite so that it would withstand the stresses of operation without breaking or throwing the blades out of alignment. In this connection it is said he specified that his lithotrite must flatten a one inch ball of lead. The present author has not found this specification in any of Bigelow's writings: perhaps it is merely part of the folklore of the Massachusetts General Hospital which has been passed along by word of mouth. He shaped the blades so that there would be a minimum risk of grasping the bladder when engaging the stone, and put triangular notches on the male blade which discharged stone fragments laterally avoiding the danger of clogging. Clogging had been one of the serious difficulties with previous instruments for when the blades could not be thoroughly closed the withdrawal of the lithotrite resulted in laceration of the urethra.

Bigelow also made improvements in the evacuator. Here his chief contribution was the use of straight tubes with large caliber. All previous evacuating tubes or catheters were so small that only sand could be washed out so that stone fragments were generally left in the bladder. Bigelow was emboldened to use tubes having a caliber of 28 to 32 French because of the recent observations by Otis that the urethral channel was much larger than had previously been believed.

He enunciated the principle of crushing and removing all of the calculus at one sitting and called the complete operation *Litholapaxy*. Hugh Cabot stated that this word was coined by the Autocrat of the Breakfast Table who gave us the word *anesthesia*, but none of Bigelow's writings credit Holmes with its origin. Bigelow asserted and demonstrated that a prolonged operation under anesthesia which accomplished its purpose was less damaging to the bladder and safer for the patient than multiple stage lithotripsy which was the practice of the day. His writings on the subject between the years 1878 and 1883 were convincing and his doctrines were widely accepted. The soundness of these principles is demonstrated by the fact that litholapaxy is performed today with the same instruments and techniques that Bigelow described three quarters of a century ago.\*

Additional developments have been made in the design of lithotrites since the invention of the cystoscope adding vision to the instrument. Hugh Young was the first urologist to design such a lithotrite and there have been many others since who have developed instruments of this type. Many urologists have thought that the advantages gained by adding vision to the lithotrite are outweighed by structural weakness and loss of flexibility and the individual who is skilled in the use of the old type lithotrite finds little need for them. However, today their use has been so widely accepted that some urologists serve their apprenticeship

\* Students of the subject will find an illuminating and historically valuable commentary on Bigelow and his contribution to lithotripsy in an editorial that appeared in *The Lancet*, 1: 149-150, January 28, 1882. This has long been buried under the anonymity of editorial comment.

without being trained in the venerable art of Bigelow. This situation has prompted your essayist in the selection of a title, and it is hoped that the present remarks might stimulate some of those not trained, to interest themselves in the art.

There are many descriptions of the technique of litholapaxy and there is nothing new to add to the subject but a recital of some of the particulars may be apropos since the present author learned the operation under the preceptorship of a master who was cradled in the Bigelow tradition.

There are certain limitations upon the scope of operation such as the presence of other lesions or conditions which of themselves call for opening the bladder. The size of the urethra must be adequate for easy accommodation of the instruments. In this connection it is interesting to recall the historic fact that Bigelow advocated the performance of perineal urethrotomy for litholapaxy when the pendulous urethra was too small for the lithotrite and evacuating tubes. The manoeuver was revived in our day by Gershom Thompson for the performance of endoscopic prostatectomy in cases having a small urethra.

Excessive size or number of calculi will also influence the selection of this procedure. Some lithotomists with great experience as well as robust hands are willing to attack stones of large size but most of us are respectful of calculi larger than 3 or 4 cm. in size. Plurality does not contra-indicate operation for several small calculi can be crushed and evacuated with greater facility than one large stone having an equal aggregate mass. Bladder capacity is another factor of importance for it is not safe to perform litholapaxy unless the bladder will hold 100 cc or more of fluid. If the bladder in the unanesthetized patient will accommodate 100 cc it is safe to assume that the capacity will be at least that much during anesthesia, and when spinal is used most bladders will demonstrate an increase in capacity. There is, however, the exceptional circumstance in which the bladder goes into tetanic contraction during anesthesia and any consideration of lithotritry or, for that matter, prostatic resection must be abandoned. Fortunately, this type of reaction is a rarity.

Prostatic enlargement does not contra-indicate the performance of litholapaxy if the surgeon believes that the situation is one that can be handled by transurethral resection at the same operation. However, the urologist must bear in mind that the co-existence of prostatic enlargement and vesical calculi does not necessarily comprise an indication for prostatectomy. Indeed, our preceptors advocated that patients who had both conditions were best treated by litholapaxy alone if there was only a small amount of residual urine even though the patient suffered a major disturbance in function. Many such patients will become asymptomatic and free from residual urine after removal of the calculus. When both are planned it is advisable to deal first with the calculi, then the prostate gland.

The lithotrites that are in use today are essentially the same as those used in Bigelow's time. A few years ago there were none being manufactured but now, fortunately, their construction has been resumed. Present day lithotritists have the advantage of using the modern resectoscope which allows ready inspection

of the bladder; and its large sheath, abetted by the Ellik evacuator, serves efficiently in removing debris from the bladder.

The first step in performing the operation is to fill the bladder to capacity with fluid, and today it is standard practice to employ a non-hemolysing solution. Many urologists prefer to inspect the bladder at the beginning of operation and the resectoscope serves this purpose satisfactorily. The bladder meanwhile is filled with fluid which can be left in when the resectoscope is withdrawn. Occasionally the contents of the bladder are evacuated spontaneously in the anesthetized subject and this, of course, would interfere with the safe manipulation of the lithotrite. Its occurrence can be prevented by tying a small rubber catheter about the base of the penis.

Introduction of the lithotrite is somewhat different from that of the ordinary steel sound because of the instrument's short beak and abrupt angle, and the tip sometimes inclines either above or below the membranous urethra interfering with its entry. This difficulty can usually be avoided by applying pressure on the heel of the instrument in the perineum using the fingers of one hand. After the beak of the instrument has passed the triangular ligament, the handle is depressed and a minimum of force will cause the lithotrite to glide on into the bladder. Its presence in the bladder will be determined by rotating the instrument first one way then the other. Failure of the instrument to rotate freely may indicate that the tip is in a dilated prostatic urethra and not the bladder, for the beak of the instrument can occasionally be rotated in a capacious prostatic urethra but not with freedom.

With the instrument properly inserted the handle is now raised so that the heel comes to rest on the floor of the bladder; then gentle pressure is applied downward so as to cause a depression of the bladder floor so that the stone will roll into it (fig. 1, A). The jaws are now opened to the fullest extent possible and then closed with gentle pressure. Usually the stone will be engaged in the first attempt but if not the maneuver is repeated. If continued efforts in the original position fail to engage the stone, the jaws should be again opened with the instrument held strictly in the middle position, then rotated first to one side and then the other, attempting to grasp the stone. If now the calculus has failed to become engaged it is because it lies either below or above the instrument. If below it is apt to be due to prostatic enlargement (fig. 1, B). In this case the instrument should be opened again in the midline position and rotated so that the jaws point down. If carefully executed this maneuver will usually be effective in grasping the stone if it is in the retroprostatic pouch (fig. 1, C). There is no great danger in this inverted maneuver for Bigelow fashioned the jaws of his lithotrite in such a way that it is virtually impossible to pick up the wall of the bladder provided it is reasonably distended. Should the search for the stone fail to discover it on the floor of the bladder it may be assumed that the stone has moved upward into the fundus so the handle of the instrument is depressed to permit exploration in that area with the blades opened.

When the stone has become engaged between the blades the lock is at once fastened, then the handle is brought into the median position and the lithotrite

rotated first one way then the other or pushed forward and backward to be certain that the stone is not attached to the bladder and that no tissue has been caught up by the instrument (fig. 1, *D*). Only when this freedom of motion has been determined should the jaws be screwed home by turning the handle. Occasionally the first crushing of a stone will cause it to shatter completely into fine sand but usually several applications are required to obtain a final subdivision of the stone but on each occasion the surgeon must bring the instrument back to the median

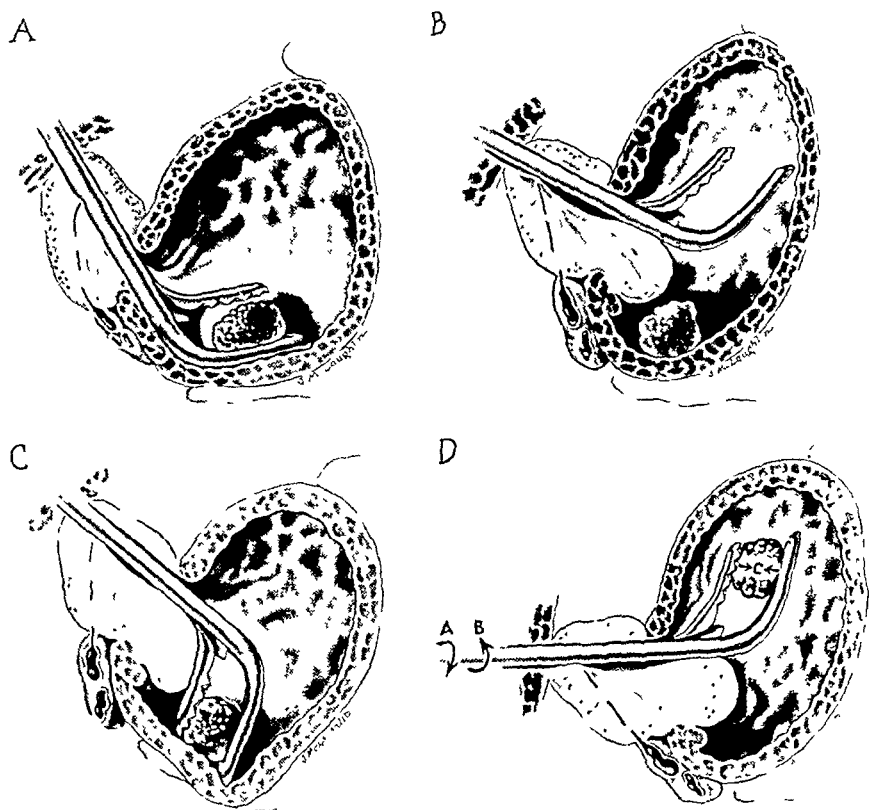


FIG. 1

position and rotate it before applying force to the blades. In the process of pulverizing large stones the debris may become so considerable in amount as to interfere with engaging of large fragments. Should this occur it may be necessary to wash out the detritus before continuing with complete subdivision of the stone.

When the lithotrite is removed from the bladder the blades must be completely closed since any separation of them by debris may cause laceration of the urethra. Complete freeing of the instrument may be attained by screwing it firmly shut, and then opening and closing the blades several times until their metal surfaces are felt to come in contact. Great care must be exerted in the avoidance of urethral injury during operation, both in this detail as well as in the

frequent use of lubricants during operation. Furthermore, the urologist will be wise to perform perineal urethrotomy rather than compromise with the possibility of damage whenever the urethra seems too small for the instruments.

When finally the surgeon is unable to enage any more fragments in the lithotrite he is ready to use the evacuator. The standard size McCarthy resectoscope sheath is recommended for this purpose, and after it has been introduced it is well to allow the fluid in the bladder to flow out. This will carry a considerable amount of debris with it. Then the Ellik evacuator, filled with fluid, is attached and fluid from the irrigating reservoir is allowed to enter and partially fill the bladder by opening the valve on the resectoscope sheath. The rapid in-and-out rush of fluid necessary for efficient evacuation of debris requires that the bladder not be empty at any time, but if too full there will be the risk of damaging the bladder by overdistention.

After all the debris has been washed out the evacuator is disconnected and the resectoscope working element inserted for inspection of the bladder. If fragments of stone are present the resectoscope is withdrawn leaving the bladder distended and the remanants are pulverized with the lithotrite. When all fragments of stone have finally been removed there will often be a layer of putty-like material covering the trigone. This is probably made up of a mixture of lubricant and sand from the calculus. It does not wash out but can be scraped from the bladder floor quite easily by the resectoscope loop without, of course, using the electric current. On final inspection of the bladder it is particularly important to determine whether any diverticula are present and to evacuate any debris that they might contain. This can be done by inserting the tip of the sheath into the diverticulum under direct vision, then using the evacuating syringe. After operation the patient is left on catheter drainage for one or three days depending on whether or not a transurethral prostatectomy has been done. ¶

This brief essay on litholapaxy has been presented in the hope that we who have inherited the operation will not allow it to become a lost art; nor should we regard its great simplicity with desultory casualness. Bigelow\* said this of litholapaxy; and his remarks are amazingly applicable as well to transurethral resection which also uniquely belongs in the realm of urology: "I know of no other surgical operation in which a little want of skill or of care is so insidiously liable to fatal accident. The skill here is of a peculiar kind; and though a surgeon may use a knife well, it does not follow that he also uses a lithotrite well."

\* Boston Med. & Surg. J., 102: 30-34, 1880.

## BLADDER ENLARGEMENT THROUGH ILEOCYSTOPLASTY

JEAN CIBERT

*From the Clinique Urologique Université de Lyon, Hôpital Edouard Herriot, Lyon, France*

In 1950 a colleague, R. Couvelaire, informed me of the results he had obtained with ileocystoplasty used for enlarging a bladder contracted by chronic tuberculous cystitis. Since that time, I have performed this operation 18 times. These cases will be published in *Lyon Chirurgical*.

In this report, I wish to show the x-ray films of one of my patients. The operation was performed in June 1951; therefore it is too recent to give a valuable opinion about it; but the favorable improvement observed in the kidney seemed sufficiently striking to justify its publication now.

### CASE REPORT

Mr. M. was aged 31 years. The primary infection with severe manifestations occurred in 1936; in 1937 pulmonary tuberculosis was discovered; in 1943, tuberculous cystitis. The patient was admitted to Pavillon V in September 1943 with intense frequency. Right nephrectomy performed after urography (ureteral catheterization impossible). The operation was followed by slight and transient improvement of cystitis. In 1944, perineal abscess; incision; cystitis unchanged; same condition of bladder as in 1945; urography showed that the function of the left kidney was normal; the ureter, renal pelvis and calyces were normal.

The patient was re-admitted in Pavillon V on June 15, 1951. His general condition was poor. He had painless micturition every 2 hours during the night, every 1 or 2 hours in the day; every fortnight, approximately, and for 4 or 5 days, painful micturition every 10 minutes. Rather pronounced incontinence during the night was present; during the day he complained of occasional pain in the left kidney. Febrile episodes occasionally reached to nearly 102°F.

Pus cells and *Escherichia coli* were present in the urine. Blood urea, 42. On excretory urography the left kidney was visualized in the first film; the only dilated calyces that were visible were as big as one hazel nut; the renal pelvis, ureter and bladder were not visualized. Urethrocytography disclosed a normal urethra and vesical neck, moderate bladder contraction and reflux on left side with marked ureteral dilatation (fig. 1, A and B).

I suggested ileocystoplasty; the purpose was to reduce frequency, to relieve incontinence, and above all, to save the remaining kidney.

After intestinal preparation and injection of 20 gr. streptomycin, the operation was performed on June 25, 1951. The incision extended from the pubis to the umbilicus. The bladder, small and retracted behind the symphysis, was released from its adipose, thick, fibrous, adhesive sheath; abundant hemorrhage; careful hemostasis. Transverse opening of peritoneum for 10 cm., a little above the top of bladder. A loop of small intestine was isolated near the ileocecal angle. Between two incisions a piece of ileum was isolated, 40 cm. long. Partial

Accepted for publication June 6, 1952.

release of mesentery. Reconstruction of ileal continuity through end-to-end anastomosis. Closure of both ends of the loop (deep layer with gut, superficial with silk). The loop was lowered against the bladder. The peritoneum was closed by suture.



FIG 1 A, urethrocytography prior to operation showing contraction of bladder and enormous ureteral backflow B, 15 minute excretory urogram prior to operation C, urethrocytography 3 months after operation Note enlarged capacity of bladder as well as notable reduction of ureteral backflow D, 15 minute excretory urogram 9 months after operation Pyelogram almost normal Note normal appearance of pelvic ureter New bladder is visible.

The loop being thus excluded from the abdominal cavity, a transverse opening of the bladder was made on its dome which was about 1 cm. thick; the musculosa was fibrous; the mucosa was changed and could be recognized with difficulty;



the left ureteral orifice was widely opened; it was quite close to the top of the bladder; as in similar cases bladder contraction affected the detrusor and not the trigone.

An 22F Harris urethral catheter was introduced into the urethral meatus and pushed down into the bladder; its tip was cut. A ureteral catheter was introduced into the ureter up to the renal pelvis; the other end of the catheter was introduced into the cut end of the Harris catheter and pushed out through it, from bladder to urethral meatus.

At this time the anastomosis was carried out. The loop was widely opened on its free edge. The bladder was anastomosed to the intestine with interrupted sutures (muco-mucous layer with catgut, musculo-muscular plan with silk).

Urine recovered from the left kidney by catheter showed pus, *B. coli*, no Koch bacillus; guinea pig inoculation negative.

The first 2 days after operation, some meteorism, and nausea. On the fourteenth day, an infected hematoma was drained. Urethral and ureteral catheters were removed on the fifteenth day; urinary fistula on the nineteenth day, and an indwelling catheter was re-inserted until the twenty-third day. Shortly afterward the patient had two profuse attacks of hematuria with clots.

The patient left the hospital on July 31 (thirty-sixth day). Frequency: 1 hour  $\frac{1}{2}$  to 2 hours at night; 1 hour in the day. No pain; no incontinence.

He was examined again on September 18, about 3 months after the operation. He had gained 8 pounds. He could wait from  $1\frac{1}{2}$  hours to 2 hours between micturitions. He had not had any attacks of acute cystitis, nor any fever. The desire for micturition was normal, as well as the size and force of the stream. Micturition is sometimes effected in two attempts. Excretory urography disclosed good renal function, marked decrease in the dilatation of the calyces; the ureter and bladder were not visible. Cystography: bladder capacity, 210 cc; persistence of the ureteral reflux; ureter not so dilated as before operation (fig. 1, C).

The patient was examined again on March 20, 1952 (9 months after operation). His general condition was excellent; his weight had increased by 28 pounds. He resumed his work in November. From 9 p.m. to 7 a.m., 3 micturitions; intervals from 2 to 3 hours in the day. Urine is slightly turbid (pus, bacilli) with long intestinal mucous filaments. I was favorably surprised by excretory urography with complete recovery of renal function, and almost normal aspect of pyelogram and above all a return to a normal condition of the ureter with return to normal caliber and tonicity (fig. 1, D). I have not made a cystogram to investigate whether reflux is still present or not; urography allows us to presume that, if it still exists, it must not be important any longer. The clinical results were confirmed on July 18, 1953 as well as radiological results.

Out of the 18 patients upon whom I performed ileocystoplasty, Strassmann's and Scheele's "ringplastik," four died from the operation. All others but two have obtained an improvement in function. The x-ray improvement has been usual, but never so striking as in the aforementioned case.

Therefore, I am of opinion that enterocystoplasty should take a place among the processes for treating chronic tuberculous cystitis which cannot be cured by nephrectomy.

In tuberculous chronic cystitis which cannot be cured by nephrectomy the surgical treatment is double in purpose: First, disability caused by intense frequency, generally painless at that phase, must be suppressed, and also the incontinence, which is then progressively developing. It is the functional purpose of the treatment. Secondly, the remaining kidney must be protected, for contraction comes to a fatal end almost in all cases by uremia. That is the vital purpose of the treatment.

It has been a common belief that terminal uremia of tuberculous cystitis not cured by nephrectomy means the destruction, without recourse, of the secondary contaminated, remaining kidney by tuberculosis. In fact bilateralization is not the rule; frequently the destruction of the remaining kidney results also from the sole hydrostatic consequences of the contracted cystitis which are reversible for a long time on a parenchyma which often remains, to the end, free from tuberculous lesions.

In fact the persistence of cystitis after nephrectomy generally prevents the evacuation of urine from a healthy kidney; above the bladder, the ureter is dilating downward to upward; a ureterohydronephrosis develops; a corollary of the stasis is a gradual thinning of the parenchyma and sclerosis; then insufficiency of the secretory function of the kidney, whether it is contaminated by tuberculosis or not.

Ureterohydronephrosis from cystitis is caused by alteration of the outlet of the ureter into the bladder. Sometimes it is dilated (*uretère forcé*) and through it, it is the intravesical pressure that constitutes itself the agent of ureteropyelocalyceal dilatation. More rarely, involved in the vesical sclerosis or affected by inflammatory lesions, it contracts.

In order to be able to accomplish both those aims, enterocystoplasty is the best process to be applied.

It is preferable to cutaneous ureterostomy, a benign operation, which protects the remaining kidney, but replaces the vesical infirmity by another one, which indeed, is more easily sustained. Cutaneous ureterostomy must not be done unless there is obstruction of the pelvic ureter.

Enterocystoplasty is preferable to ureterosigmoidostomy which has certainly the same danger; indeed, ureterosigmoidostomy, even in favorable cases where the ureter has kept its tonicity, is uncertain as regards late results; the ceaseless modifications of technique with the purpose to avoid the risk of stenosis of the ureterosigmoidal anastomosis do not seem to me, to have done away with that uncertainty yet.

Another advantage of enterocystoplasty is that, if the late result is compromised, it is always possible to come to cutaneous ureterostomy.

#### SUMMARY

A case of ileocystoplasty is presented. The operation was performed for tuberculous cystitis persisting after nephrectomy, for the suppression of frequency and incontinence, on one hand; and to protect the remaining kidney from destruction, on the other hand.

Although they are recent, x-ray results justify the publication of this case,

since they prove that the operation is capable of ensuring the return to normal renal function and ureteropyelocalyceal morphology, while acting effectively on frequency, incontinence and the general condition of the patient.

When treating chronic cystitis (tuberculous or not), enterocystoplasty seems to be superior to ureterosigmoidostomy and cutaneous ureterostomy. The latter operation is indicated only in certain cases: extensive stenosis of the lower end of the ureter (when the stenosis is localized in the ureteral outlet, the ureter cut off above the stenosis can be inserted into the ileal loop, communicating with the bladder) and when enterocystoplasty failed.

*7, Place Bellecour, Lyon, France*

## THE CORRELATION OF ELECTROMYOGRAPHIC RECORDS WITH NEUROGENIC DYSFUNCTION OF THE HUMAN URINARY BLADDER

W. H. BOYCE,\* E. L. COREY, S. A. VEST AND C. R. FRENCH

*From the Departments of Urology and Physiology of the University of Virginia Medical School,  
Charlottesville, Va.*

Bioelectric action potentials from the human urinary bladder may be recorded in wave form by use of intravesical contact electrodes and the Grass electroencephalograph.<sup>1, 2</sup> A method for synchronous recording of these potential shifts and accompanying changes in intravesical pressure has been described.<sup>3</sup> The present report is based on the application of this method of study to 74 patients with neurogenic dysfunction of the bladder. Sixty-one of the group had traumatic injury of the spinal cord, 7 had advanced central nervous system syphilis, 4 patients had multiple sclerosis, and 2 adults had congenital meningomyelocele involving the sacral segments of the cord.

### METHOD

The patient was placed on an examining table in stirrups and an electrode carrier† containing three channels was passed into the bladder (fig. 1). Two ball electrodes of sterling silver measuring 2.0 mm. in diameter and mounted on carefully insulated spring leads were then brought into contact with each lateral bladder wall. The third channel was connected to either a water manometer or a Statham strain gauge and an irrigating flask with Murphy drip was arranged so that various degrees of bladder filling (60–90 drops/minute) with a non-electrolyte solution could be obtained. A pre-nasal thermocouple and electronic control unit‡ for the Statham strain gauge were also led into the Grass model III-C electroencephalograph. Synchronous records of electropotential shifts from the bladder electrodes (action potentials), nasal thermocouple (respirations), and Statham strain gauge (intravesical pressure) could thus be obtained.

### THE NORMAL BLADDER

The normal bladder was found to develop rhythmic shifts in electropotential which occurred at an average rate of 2.4 per minute (fig. 2, 1, table 1). On the

Supported in part by the Fluid Research Fund of the University of Virginia Medical School.

Accepted for publication October 1, 1952.

\* Present address: The Bowman Gray School of Medicine, Winston-Salem, N. C.

† Electrodes and carriers provided by Mr. Frederick J. Wallace of American Cystoscope Makers, Inc., New York, N. Y.

‡ Made available through a grant-in-aid by the Committee on Research, Council on Pharmacy and Chemistry of the American Medical Association.

<sup>1</sup> Boyce, W. H.: Bladder electromyography: A new approach to diagnosis of urinary bladder dysfunction. *J. Urol.*, 67: 650, 1952.

<sup>2</sup> Corey, E. L., Boyce, W. H., Vest, S. A. and French, C. R.: Electropotential changes in human urinary bladder: A method of measurement. *J. Applied Physiol.*, 3: 631, 1951.

<sup>3</sup> Corey, E. L., Boyce, W. H. and French, C. R.: Electropotential and pressure variations in normal human urinary bladder. *J. Applied Physiol.* (In press.)

basis of previously presented evidence it was concluded that these electropotential shifts were associated with muscular activity of the detrusor.<sup>1, 2, 3</sup>

Changes in intravesical pressure which resulted from detrusor activity were consistently accompanied by the typical A-B wave of the electromyogram, but this A-B wave was not observed in association with extrinsic pressure changes which were unaccompanied by muscular contractions of the bladder; for example, cough, manual pressure upon the abdomen, or elevation in base-line intravesical pressure as the bladder was slowly filled. However, not all muscular activity of

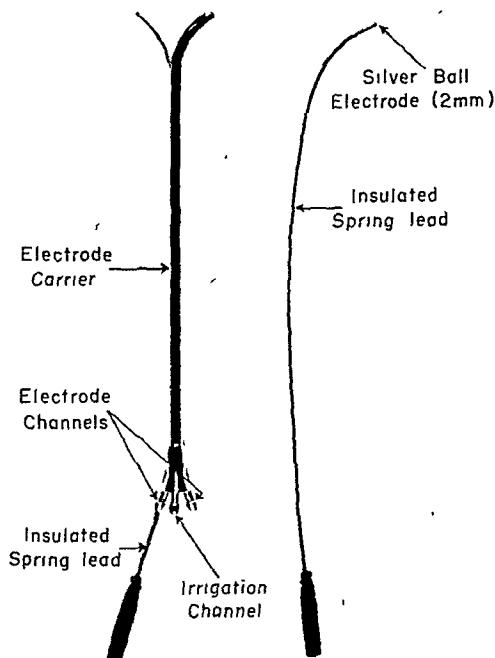


FIG. 1. Three channel electrode carrier with one electrode in position for use and one removed.

the bladder, as evidenced by electropotential shifts, was accompanied by demonstrable changes in intravesical pressure. This has led us to the conclusion that segmental contractions may occur which, by virtue of the compensatory action of different regions of the viscus, result in a failure of total bladder response as detectable by manometric measurement. These segmental contractions were most commonly observed when the viscus contained less than 50 cc of fluid.

The E.M.F. developed in association with spontaneous contractions of the bladder was not always quantitatively proportional to the changes in intravesical pressure. This is in accord with the concept that not all muscular activity of the bladder results in a total response of the detrusor and also conforms with the known disparity between the E.M.F. of action potentials and the mechanical force exerted by isolated preparations of smooth muscle.<sup>4, 5</sup> Furthermore, the

<sup>4</sup> Bozler, E.: The relation of the action potentials to the mechanical activity in intestinal muscle. *Am. J. Physiol.*, **146**: 496, 1946.

<sup>5</sup> Fischer, E.: Vertebrate smooth muscle. *Physiol. Rev.*, **24**: 467, 1944.

force of contraction of smooth muscle is dependent, within physiological limits, upon its initial length.

Voluntary efforts to void consistently produced characteristic changes in both electropotential (fig. 3, A) and intravesical pressure.<sup>3</sup> An effective voiding contraction of the bladder would seem to require an integrated response of the greater portion, if not all, of the detrusor. This contraction is apparently preceded by the A wave of the electromyogram which is associated with a decrease in

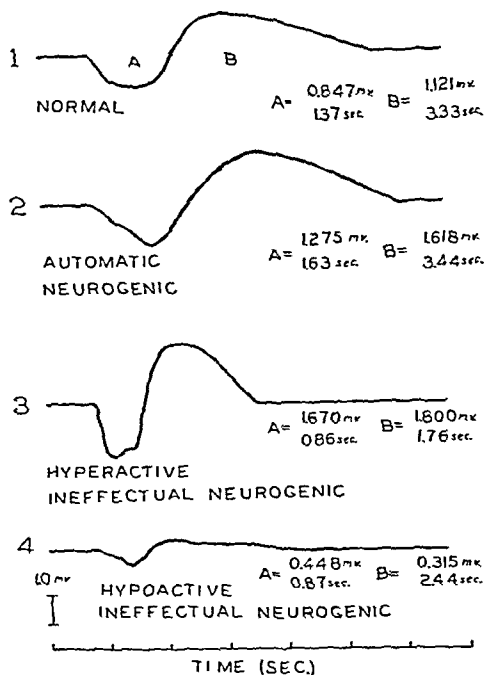


FIG. 2. Spontaneous electromyograms from normal and from various stages of recovery of neurogenic bladder following spinal cord injury. These are reconstructed on same time and E.M.F. scales and are based on average measurements listed in table 1. Scale reproductions are utilized since the original records are approximately equal in size due to variations in amplification by the electroencephalograph. 1, Spontaneous activity of the normal bladder. 2, Automatic neurogenic bladder. Note similarity to normal. 3, Hyperactive neurogenic bladder characterized by marked increase in E.M.F. and shortened duration for both A and B waves. 4, Hypoactive neurogenic bladder characterized by reduced E.M.F. and duration for both waves. Low E.M.F. generated during contraction (B wave) is outstanding characteristic.

intravesical pressure. These changes are followed by the B deflection of the electromyogram which is coincident with increased pressure within the viscus. The peak intravesical pressure was found closely to coincide with the peak E.M.F. of the B wave and both occurred just prior to the initiation of the flow of urine through the urethra. The intravesical pressure then subsided to some extent as the B wave approached the base line. Once voiding had begun, the intravesical pressure was observed to drop rapidly and smoothly, and to be unaccompanied by electropotential changes until near the termination of the act when one or more typical A-B wave complexes developed. If the patient concentrated on forceful micturition, one or more sustained monophasic electromyographic C

, similar in sign to the B deflection, occurred during the expulsion of urine , A). These observations suggest that urination is initiated by a strong ction of the detrusor as a whole, but may then proceed as a result of the ity of the bladder wall, aided perhaps by gravity as well as increased intra- inal pressure. Subsequent active contractions of the detrusor as a whole into play near the termination of the act or when the patient concentrates eful urination. The succession of electromyographic deflections occasionally ed when the patient attempted forceful urination suggests that segments detrusor may become successively excited in an integrated manner.

1. *Comparison of spontaneous electromyograms of bladder obtained from normal and from various stages of recovery following traumatic injury of the spinal cord*

|                               | A WAVE   |                 | B WAVE   |                 | C WAVE                          |                 | WAVES PER MINUTE |
|-------------------------------|----------|-----------------|----------|-----------------|---------------------------------|-----------------|------------------|
|                               | Duration | Potential Shift | Duration | Potential Shift | Duration                        | Potential Shift |                  |
|                               | sec.     | mv.             | sec.     | mv.             | sec.                            | mv.             |                  |
| l bladder from 12)            | 1.37     | 0.847           | 3.33     | 1.121           | 3.54                            | 0.860           | 2.4              |
| atic-reflex urogenic) from 7) | 1.63     | 1.275           | 3.44     | 1.618           | 7.10                            | 1.608           | 1.5              |
| ctive urogenic) from 16)      | 0.86     | 1.760           | 1.67     | 1.800           | Present only in advanced stages |                 | 3.4              |
| tive urogenic) from 18)       | 0.87     | 0.448           | 2.44     | 0.315           | Absent                          |                 | 0.5              |

THE NEUROGENIC BLADDER

*inactive (shocked) bladder.* This condition was observed immediately following sectioning lesions of the spinal cord, regardless of the site of the lesion. The pressure curve (tonus) was observed to remain within normal limits as noted by Nesbit.<sup>5</sup> We have not observed a completely inactive bladder in the patients we have examined within 1 to 10 days after injury. At least one wave could be elicited in 20 to 30 minutes of observation, especially if the bladder contents were varied slowly. These waves were of short duration, of low amplitude, and unaccompanied by any demonstrable pressure changes; therefore, for practical purposes, the condition may be considered one of bladder atony.

*hypoactive, ineffectual, neurogenic bladder.* This type of activity was encountered in the early stages of recovery of muscular activity after the "inactive (shocked)" period. Patients with complete lesions of the cauda equina or sacral segments were not observed to progress beyond this hypoactive type. The rate of muscular activity in the resting bladder averaged 0.5 contractions per minute. The rhythm was irregular and long periods of quiescence were observed. The A wave averaged 0.448 mv. peak E.M.F., and 0.87 second in duration.

tion, while the B deflection averaged 0.315 mv. and 2.44 seconds (fig. 2, 4). It seemed significant that the E.M.F. of the A wave was of greater value than the B wave in the group as a whole, since this constituted a direct reversal of the A to B ratio found in both the normal and hyperactive types of bladder ac-

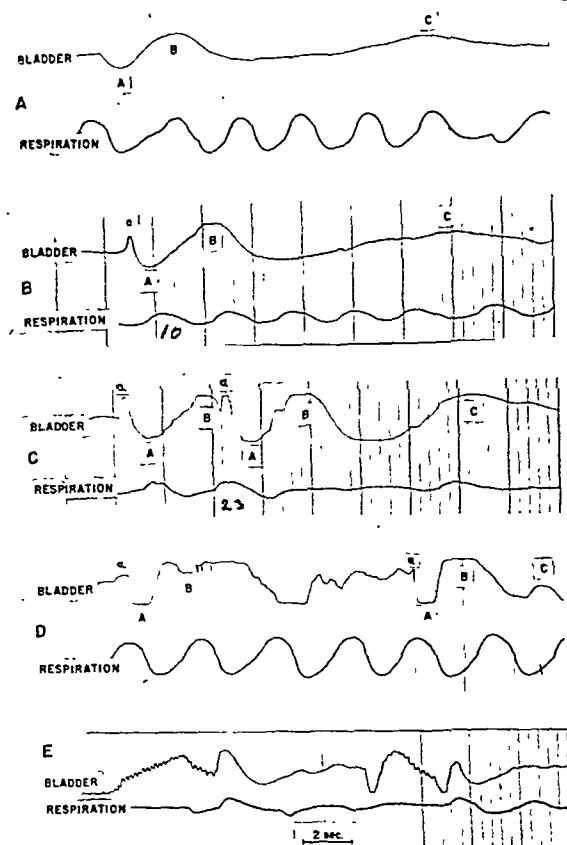


FIG. 3. Electromyograms representative of "voiding" contractions of normal and various types of neurogenic bladder activity. These are photographs of actual records, hence time scale is same for each but E.M.F. scale is variable, for example, 1 mm. deflection in III-D represents  $5 \times$  the E.M.F. of a mm. deflection in A. A, normal bladder, note variations in respiration at beginning and end of micturition. B, automatic bladder, voiding reflex initiated by slowly filling to critical capacity. C, automatic bladder, voiding reflex initiated by stimulation of cutaneous "trigger" area. D, spontaneous spasm of hyperactive bladder with small capacity and little residual. (This was accompanied by "pressor" symptoms.) E, attempt to void by patient with physiologically incomplete lesion and hyperactive but atonic bladder. (Electrodes near bladder base.)

tivity. A complex of A-B and C waves characteristic of a voiding effort was not observed in this group, although some patients with functionally incomplete lesions were able to produce an A-B wave of low E.M.F. when instructed to void.

Measurable changes in intravesical pressure rarely occurred in association with shifts in electropotential, and were very slight (3-5 mm. Hg) when present.



The initial diminution in pressure associated with the A wave was usually present when measurable changes in pressure did occur.

This type of bladder activity was also observed in patients who had experienced prolonged suprapubic or urethral catheter drainage without tidal irrigation, or who had had prolonged cystitis with bladder encrustations. It was also characteristic of those patients who had inadequate urinary drainage with the development of chronically overdistended bladders, loss of muscular tone, a large residual urine, and usually with cellulites and diverticula of the bladder wall. The hypoactive bladder is therefore characteristic not only of the early stages of return of muscular activity but also of lesions of any level of the spinal cord where treatment has been grossly inadequate.

Those patients with advanced central nervous system syphilis (either tabetic or congenital) who had a large residual urine and a marked increase in bladder capacity with cellulites and diverticula were observed to exhibit an A-B wave complex indistinguishable from that of the hypoactive bladder of cord injury (fig. 2, 4). The electromyographic records from these luetic patients were distinguished by two principal characteristics: the rate of activity of the empty bladder was greater (av. 2.7/minute) than in the bladder following cord injury, and a voiding complex of A-B-C waves could usually be obtained in these individuals, although it frequently required a number of attempts on the part of the patient.

*The hyperactive, ineffectual, neurogenic bladder.* This type of bladder activity may be regarded as the intermediate stage between the hypoactive and the automatic-reflex bladder. It was noted that cord injuries between the eleventh dorsal and third lumbar segments demonstrated a tendency to remain stable at this stage of functional activity, whereas lesions superior to the tenth dorsal segment were more likely to progress to the automatic type under appropriate therapy.

The typical electromyogram as illustrated in figure 2, 3 is characterized by a relatively high E.M.F. occurring in a short time interval. As the bladder was gradually filled there was an increase in frequency which may be described as "bursts" of activity, in which one wave was scarcely ended before a second began. These "bursts" were usually interspersed with periods of several minutes of complete quiescence. In some patients a sustained increase in intravesical pressure for periods of as much as four minutes was observed to coincide with this type of muscular activity and to regress as these "bursts" subsided.

Bladder spasm was characterized by sharp deflections of the oscillograph both above and below the base line, with very large E.M.F. changes which have been recorded as high as 8.0 mv. (fig. 3, D).

Further evidence that more than one segment of the bladder may undergo excitation and contraction at different time intervals is illustrated in figure 3, C. Not infrequently the hyperactive bladder and occasionally the automatic bladder have been observed to produce a second A-B wave complex superimposed upon the B wave already in progress. The logical explanation for this phenomenon is a dissociation of muscular activity of segments of the bladder somewhat analogous

to the "heart block" encountered in cardiac physiology. Inspection of figure 3, *C* indicates that a second "a" wave began 4 seconds after the first "a" wave and while the initial B wave was in progress. This would indicate that excitation of the first segment of the bladder occurred 4 seconds before excitation of the second segment and the ensuing B and C waves represent the vector sum of the E.M.F. from all of the excited muscle cells.

Patients with incomplete neurologic lesions involving the bladder have been observed to have a large residual urine and to void only small quantities. The routine cystometrogram indicated a marked decrease or absence of bladder tone and little or no increase in intravesical pressure with voluntary efforts to void. Hyperactive type contractions of the base of the bladder were demonstrated to occur by electromyography (fig. 3, *E*), although no muscular activity was demonstrable when the electrodes were placed in the dome of the bladder. Thus the routine cystometrogram would indicate a completely inactive detrusor, whereas the electromyogram indicated active contractions of the segments of the bladder near the base. The intravesical force resulting from these contractions was apparently dissipated against the inactive dome.<sup>6</sup>

It was noted that the majority of the patients in the "hyperactive" group had a small bladder capacity with little or no residual urine, although about one third of the group had residual urine of 30 to 550 cc. Pressure changes in association with the electropotential shifts were most commonly observed in patients with little residual urine and an increase in bladder tonus. It was further observed that the diminution in intravesical pressure typically accompanying the A deflection of the normal bladder was absent or too minute to be accurately measured in this group as a whole.

*The automatic-reflex bladder.* Only 7 patients were studied who were considered to have attained this ideal stage of "bladder training." All of these had had transecting lesions of the cord at the level of the first to the tenth dorsal segments from 7 months to 14 years prior to study. Two of these patients were under observation from the time of injury until the development of this stage. The critical bladder capacity varied between 240 and 500 cc, interval voiding was practiced and residual urine was less than 40 cc. All patients were free from active urinary tract infection or calculi, and excretory urograms were without gross abnormality. Bladder tonus was slightly to moderately increased. Some degree of detrusor hypertrophy seemed to be present as judged by minimal to moderate trabeculation visible on cystoscopic examination, but no patients with true celluloses or diverticula were included in this group.

The electromyogram of the empty bladder was characterized by the prolongation of the electropotential shifts (fig. 2). Frequency of contractions averaged 1.5 waves per minute, with an almost constant rhythm. As the bladder was slowly filled, the rhythm became less regular and periods of quiescence were observed. When bladder filling approached critical capacity, the rhythm again became similar to that of the resting bladder; and further distention resulted in a reflex

<sup>6</sup> Muellner, S. R.: The physiologic components of the urinary bladder. *New Eng. J. Med.*, 241: 769, 1949.

voiding contraction with marked rise in intravesical pressure and passage of urine about the electrode carrier. This voiding contraction was characterized by a typical A-B wave and was followed by a single C wave, or series of monophasic waves (fig. 3, *B*, *C*). More rarely one or two typical A-B wave complexes appeared as the voiding reflex subsided.

Measurable pressure changes did not accompany the majority of the spontaneous shifts in electropotential (contractions). When pressure changes occurred, the A wave was followed by a definite diminution in intravesical pressure which reached a maximum of 16 mm. Hg in the resting bladder, and as much as 28 mm. Hg prior to a reflex voiding contraction. The "latent period" or lag between the onset of the electropotential shift and the diminution in pressure was variable. This interval of time in the normal averaged 0.66 second, but in the automatic bladder was prolonged to an average of 1.21 seconds. A maximum lag of 6.8 seconds has been observed to occur between the appearance of the initial spike potential ("a" wave) and the diminution in pressure although this diminution coincided closely with the peak of the A wave. Maximum elevation in intravesical pressure always coincided with the B wave, while pressure increments coincident with the C waves were of lesser degree.

It was noted that increase in intravesical pressure due to extrinsic force did not result in micturition by the neurogenic bladder unless a contraction of the detrusor occurred, even though the intravesical pressure exceeded that developed during automatic micturition in the same bladder. This was repeatedly demonstrated during the examination of paraplegic patients whose spinal cord lesions were superior to the tenth dorsal segment. Strong manual pressure on the abdomens of these patients was observed to produce a marked elevation in intravesical pressure (72 mm. Hg) without producing either a flow of urine about the urethral instrument or A-B waves on the electromyographic record. Seconds later, by light massage or stimulation of a sensory "trigger" area we have seen the typical A-B waves develop on the electromyogram with the characteristic initial diminution and subsequent rise in intravesical pressure followed by the passage of urine in quantity through the urethra (fig. 3, *B*, *C*). We were unable to determine whether the reciprocal relationship between integrated bladder contraction and relaxation of urethral resistance was mechanical, as described by Young and Wesson,<sup>7</sup> or reflex, as suggested by Barrington,<sup>8</sup> or a combination of both.

Patients with multiple sclerosis who had not developed bladder decompensation and residual urine were found to have electromyographic records quite similar to the automatic-reflex bladder of traumatic origin. It was noted that these patients often demonstrated a bladder irritability and frequency of electropotential shifts much like the "hyperactive" bladder of cord injury but "reflex voiding contractions" occurred even in the almost empty bladder. Repeated examinations in the same patients resulted in a wide variation in the degree of

<sup>7</sup> Young, H. H. and Wesson, M. B.: Anatomy and surgery of trigone. Arch. Surg., **3**: 1, 1921.

<sup>8</sup> Barrington, F. J. F.: The component reflexes of micturition in cat. Brain, **54**: 177, 1931.

distention that could be attained before such "uninhibited" contractions occurred.

#### DISCUSSION

The status of the bladder following transecting lesions of the segmented nervous system is usually one of constant anatomic and physiologic change. The inactive (shocked) phase is followed by a return of functional activity which is at first characterized by a low muscular irritability and ineffectual contractions (hypoactive bladder). These become progressively more effective and integrated so that a period of true incontinence may result because of the uninhibited bladder contractions which seem to stem from both an increase in muscular irritability and an accelerated efferent nervous bombardment of the bladder (hyperactive bladder). Under correct management, this hyper-irritability may resolve into a "filling reflex" (gentle stretch of the muscle during physiologic distention resulting in relaxation rather than contraction) which permits bladder capacity to approach the levels of normal. An integrated contraction may then be evoked within the fully distended bladder either from the intrinsic "stretch reflex" (fig. 3, *B*) or from extrinsic sensory stimuli to the penis, perineum, legs or abdomen (fig. 3, *C*).

Comparison of electromyographic records from the same individual taken from time to time has proved to be advantageous in the clinical management of the paraplegic patient. During the inactive "shocked" stage it was considered advisable to place the patient on a system of closed bladder irrigation manually operated. This procedure was designed to prevent the overdistention that may occur if a tidal irrigation apparatus does not drain the bladder properly even for short periods of time.

As the inactive bladder began to exhibit the characteristic electromyogram of the hypoactive viscus, tidal irrigation with Suby's solution G was instituted and continued through the hyperactive stage. As the A-B wave complex increased in duration to  $\frac{1}{2}$  seconds or more, the patient was placed on catheter drainage from 7 a.m. to 7 p.m., but tidal irrigation was resumed during the night. During the day the patient was instructed to clamp the catheter, to regulate the emptying time to a capacity of as near 300 cc as possible, and to note any sensation which would indicate filling of the bladder to this capacity. As the bladder was emptied he was taught to search for sensory "trigger" areas which could initiate a reflex voiding contraction. When the electromyogram indicated a possible voiding complex of A-B-C waves, the catheter was removed. During this transitional period the judicious use of either banthine to reduce undue bladder irritability or a parasympathomimetic drug to assist interval voiding has proved an effective supplemental measure.

Figure 2 and table 1 were constructed from the average values obtained from the electromyograms of patients who were considered to occupy the "median" position in each group and who had a minimum of complicating anatomical changes within the bladder. Anatomical changes such as severe infection, encrustations, and cellulæ or diverticula result in variations in the basic form of

the electromyogram as previously reported.<sup>1</sup> This is no disadvantage in interpretation of the record since even brief familiarity with the technique permits immediate recognition of the basic wave form. Progression of the paraplegic bladder from one stage to another is gradual, so that there are all degrees of gradation between the "typical" electromyograms illustrated in figure 2. Thus the early stages of development of the "hyperactive" bladder exhibit a much slower rhythm and lower E.M.F. for both the A and B waves than do the median or typical stages listed in table 1. During the typical stage of hyperactivity the C wave is conspicuously absent, but as bladder activity progresses toward the automatic-reflex type these waves become apparent, and such deflections in this group of patients were found to average 4.5 seconds in duration, with a peak electropotential shift of 0.490 mv.

### CONCLUSIONS

Spontaneous and reflex contractions of the neurogenic bladder are always accompanied by bioelectric action potentials but if segmental in character do not always result in demonstrable changes in intravesical pressure. Micturition is the result of an integrated contraction of all or the greater portion of the detrusor in both the normal and neurogenic bladder. Normal or slightly increased detrusor tonus facilitates complete emptying of the bladder; however, tonus is an entirely separate phenomenon occurring independently of detrusor contractions and taken per se is of little value as an indication of the functional capabilities of the viscus as a whole.

A technique is described for translation of bioelectric action potentials of the detrusor into wave form. The duration and configuration of the electromyogram so obtained permit accurate distinction between changes in intravesical pressure due to activity of the detrusor from changes due to extrinsic forces. The electromyogram also gives an indication of whether the bladder contraction is complete or segmental, but simultaneous observation of a simple water manometer is confirmatory evidence and a valuable aid in interpretation of the record.

## TRANSURETHRAL RESECTION FOR THE PARALYZED BLADDER: PRELIMINARY RESULTS

FREDERICK M. JACOBS, JOHN L. BERRY AND JOSEPH C. ORMAN

The authors of this report do not presume to have knowledge not shared by others of the complex series of events culminating in the emptying of the urinary bladder. During the past decade, much significant investigation has been directed to the basic problem of micturition. However, there is not yet general agreement concerning the detailed dynamics and structure of the physiology of this elementary function, particularly of the sequence and relative importance of a number of variable factors, such as intravesical pressure, cerebral inhibition and stimulation, spinal discharge, and trigonal activity. Nevertheless, enough is known of the mechanics of normal and disordered micturition to establish a workable, rational plan of action for dealing with a paralyzed bladder which cannot force the urethral tube.

Owing to the work of Emmett, Bumpus, Thompson, and others, transurethral resection is widely accepted as a sound and logical procedure for re-establishing lost bladder function. A usefully functioning bladder must a) retain urine and b) expel urine. The residual should not exceed 50 cc and control must be good. Such a bladder can be obtained by this procedure, as this short series, and longer reports by others, conclusively show. The period of observation in this series extends from three months to three years or more. The principle of the operation is a mechanical one. After transection of the cord in man, the phenomenon of spinal shock dominates the clinical picture. The bladder reflexes, along with all reflexes below the level of injury, disappear. About 3 weeks later, depending upon the completeness of the transection, the reflexes may partially return but the return is usually not total. The micturition reflex, which depends upon the spinal reflex arc, the pons, and cerebral cortex, having been deprived of pontine and cerebral influence, is incapable of efficiently emptying the bladder. The maximum intravesical pressure is usually too low to overcome urethral resistance. Detrusor action cannot be strengthened, but urethral resistance can be weakened, so that the balance between intravesical pressure and urethral resistance can be approximately restored. Removing tissue from the vesical neck and prostatic urethra, and, if necessary, the external sphincter, accomplishes practically any desired reduction in urethral resistance. For example, a maximum intravesical pressure of 40 cm. of water cannot overcome urethral resistance of 45 cm. of water. Decreasing the urethral resistance sufficiently by transurethral resection permits the highest attainable intravesical pressure, perhaps aided by the hands and abdominal muscles, to empty the bladder. If the "resting" bladder tone remains less than the resultant urethral resistance, incontinence will not supervene. The technique of the operation has been fully described by others and need not be repeated here.

The cutting of sacral roots supplying a bladder which is already hypotonic has, curiously, been performed for the purpose of restoring bladder function.

This procedure is said to be based on the assumption that there are "inhibitory" fibers in the sacral roots which "inhibit" efficient detrusor action. No such inhibitory fibers have ever been demonstrated as far as we have been able to determine. The destruction of sacral roots may, in fact, compromise still further the already incompetent detrusor muscle activity and, moreover, this procedure ablates the tonic discharge over the internal pudendal nerve which controls the external urinary sphincter. The external sphincter therefore undergoes paralysis and atrophy, as does other skeletal muscle when deprived of its nerve supply, and its myotactic activity is irretrievably lost. Under such circumstances the occasional patient can empty his bladder, simply due to paralysis of the urinary sphincters, but consideration of the much greater majority who may thereby be denied the development of efficient bladder function by other methods points to the futility of this sort of interference. Of equal seriousness and import, the inevitable and repeated urinary infections that occur in paraplegic patients who are "studied" by spinal anesthesia, sacral block, and repeated catheterizations over periods of months, frequently result in a formidable cystitis with tremendously thickened bladder walls, urethritis, peri-urethral abscess, urinary calculi,

TABLE 1

| LUMBAR LESIONS | THORACIC LESIONS | CERVICAL LESIONS | CEREBRAL LESIONS | JUVENILE TABES | PARKINSON'S DISEASE | HYPOTONIC BLADDER, CAUSE UNDERTERMINED |
|----------------|------------------|------------------|------------------|----------------|---------------------|----------------------------------------|
| 3              | 31               | 1                | 1                | 1              | 1                   | 1                                      |

etc., increasing out of all proportion the difficulties encountered in establishing useful bladder function.

Our experience with paraplegic patients leads us to think that a critical factor in the re-establishment of vesical function is the absence of infection. "Tidal drainage" and other forms of bladder irrigation serve to minimize infection by their mechanical cleansing action, and are therefore extremely useful. However, no evidence has been advanced that tidal drainage has any particular virtue other than local cleansing of the bladder reservoir. This conclusion has been reached after repeated observations of spinal patients (approximately 700) in a Veterans Administration hospital over a period of more than 3 years.

It is apparent that the great majority of these patients will not achieve a useful bladder unless and until some procedure reducing urethral resistance is carried out. C. E. Thompson, following the suggestion of Bors, obtained limited success in temporarily re-establishing bladder function by blocking the pudendal nerves, which, of course, paralyzes the external urinary sphincter mechanism. Moreover, he achieved essentially the same degree of success by alcohol injection into the subarachnoid space of the isolated cord segment. Others have attempted the same thing by dividing the sacral roots, with results which are commensurate with the unphysiological basis of the procedure. Reference is not made here to the small spastic bladder, with spasm of the lower extremities, usually associated with an incomplete cord lesion. The capacity of this type of

TABLE 2  
c = complete  
i = incomplete

| CASE                | LEVEL OF LESION OR DISEASE                       | NUMBER OF RESECTIONS | MONTHS SINCE LAST RESECTION | URINARY RESIDUAL | CONTROL |
|---------------------|--------------------------------------------------|----------------------|-----------------------------|------------------|---------|
|                     |                                                  |                      |                             | cc.              |         |
| M.N.                | T6 i                                             | 1                    | 34                          | 0                | Good    |
| G.M.                | T4 c                                             | 1                    | 3                           | 0                | Good    |
| A.U.H.              | T6 c                                             | 1                    | 3                           | 0                | Good    |
| M.S.                | T10 c                                            | 1                    | 3                           | 0                | Good    |
| C.R.H.              | T7 c                                             | 3                    | 31                          | 0                | Perfect |
| F.W.                | L3 i                                             | 1                    | 2                           | 0                | Good    |
| O.W.                | T4 c                                             | 1                    | 3                           | 60               | Good    |
| F.R.                | L1 c                                             | 1                    | 31                          | 0                | Perfect |
| R.D.                | T11 c                                            | 1                    | 26                          | 0                | Perfect |
| J.Z.                | T10 c                                            | 1                    | 30                          | 0                | Good    |
| M.O.                | T9 c                                             | 1                    | 34                          | 0                | Perfect |
| J.F.                | T9 c                                             | 1                    | 23                          | 0                | Good    |
| C.M.                | T12 c                                            | 1                    | 14                          | 0                | Good    |
| I.C. <sup>1</sup>   | T10 c                                            | 1                    | 29                          | Complete         |         |
| N.V.                | T4 c                                             | 2                    | 27                          | 0                | Poor    |
| P.H. <sup>2</sup>   | T11 c                                            | 4                    | 18                          | 0                | Good    |
| J.L.                | T5 c                                             | 1                    | 39                          | 0                | Good    |
| C.S.                | T10 c                                            | 1                    | 34                          | 0                | Good    |
| P.W. <sup>1</sup>   | T5 c                                             | 1                    | 3                           | 425              |         |
| J.K. <sup>3</sup>   | C6 i                                             | 1                    | 3                           | 0                | Good    |
| W.L.W.              | T2 c                                             | 2                    | 29                          | 0                | Good    |
| F.H.D.              | T12 c                                            | 1                    | 32                          | 0                | Perfect |
| J.H.S.              | T11 c                                            | 2                    | 33                          | 0                | Good    |
| L.T.                | T3 i                                             | 1                    | 34                          | 0                | Perfect |
| E.W.                | T2 i                                             | 1                    | 34                          | 0                | Good    |
| D.H.W.              | L1 i                                             | 1                    | 23                          | 0                | Good    |
| W.H.H.              | T11 i                                            | 1                    | 32                          | 0                | Good    |
| G.W.S.              | T5 c                                             | 1                    | 35                          | 0                | Good    |
| I.E.D.              | T12 c                                            | 1                    | 28                          | 15               | Perfect |
| R.E.D. <sup>4</sup> | Cerebral                                         | 1                    | 34                          | 0                | Poor    |
| P.F.                | T11 c                                            | 1                    | 34                          | 100              | Good    |
| G.P.B.              | T11 c                                            | 1                    | 26                          | 0                | Perfect |
| J.L.B.              | Juvenile tabes                                   | 1                    | 18                          | 0                | Perfect |
| C.S.                | T4 c                                             | 3                    | 26                          | 0                | Good    |
| R.J.                | T4 i                                             | 1                    | 40                          | 0                | Perfect |
| C.L.B.              | L1 i                                             | 1                    | 29                          | 0                | Good    |
| H.C.P.              | T5 i                                             | 1                    | 37                          | 0                | Good    |
| H.D.W.              | Hypotonic bladder,<br>etiology undeter-<br>mined | 1                    | 9                           | 0                | Perfect |
| A.R.                | Parkinson's disease                              | 1                    | 9                           | 0                | Perfect |

<sup>1</sup> Refused further resection.

<sup>2</sup> Has been unable to empty bladder since spinal tractotomy for "pain" 16 months after resection.

<sup>3</sup> Died on OR table during chordotomy for "spasticity" three months after transurethral resection.

<sup>4</sup> Gunshot wound.



bladder, frequently less than 100 cc, may sometimes be increased to satisfactory proportions by sacral neurotomy, thereby permitting the performance of a more definitive procedure to re-establish useful bladder function. In our opinion, situations such as this exhaust the indications for sacral neurotomy in the treatment of the neurogenic bladder.

The group of spinal patients we have observed presented every degree of urinary tract infection, and the majority were complicated by large pressure sores and urinary calculi. Most had had multiple operations, such as laminectomy, rhizotomy, nephrolithotomy, nephrectomy, suprapubic cystostomy, etc. Of this group, some 60 were treated by transurethral resection, selection of cases being made solely on this basis: a bladder capacity of at least 150 cc, with a persistent urinary residual larger than 60 cc, in individuals able to withstand resection. The residual in most was complete: the bladder capacity and the residual urine were equal or approximately so. Thirty-nine of these have been adequately observed. The remainder could not be satisfactorily followed and will not be reported. One patient died 12 hours after operation from uncontrollable hemor-

TABLE 3

| TOTAL CASES | NO RESIDUAL | RESIDUAL 100<br>CC OR LESS | RESIDUAL 100<br>CC. OR MORE | CONTROL GOOD<br>OR PERFECT | CONTROL POOR | UNSATISFACTORY<br>VOIDING |
|-------------|-------------|----------------------------|-----------------------------|----------------------------|--------------|---------------------------|
| 39          | 34          | 3                          | 2                           | 35                         | 2            | 2                         |

rhage. The patients were all male adults, ranging in age from 19 to 55. Duration of injury prior to operation varied from a few months to several years. Thirty-five were cases of spinal paraplegia, and 4 were cases of hypotonic urinary bladder from other causes. Table 1 shows the lesion level or disease, table 2 shows the results in some detail, and table 3 shows the consolidated results. The numbers are too small to be significantly expressed in percentages. As used in this paper, control is "perfect" when urine is voided at voluntary intervals, with no urinary leakage between these intervals. It is "good" when urine is voided at approximately voluntary intervals, but there may be leakage when physical activity, such as getting in and out of bed, is undertaken with a full bladder, or there may be short involuntary spurts of urine under a variety of other conditions. Control is "poor" when an external device must be worn at all times to maintain dry clothing.

Our experiences seem to indicate that the subject for transurethral resection should be operated upon as soon as maximum reflex activity returns, usually within 2 to 6 weeks. Meanwhile the patient is given every opportunity to develop spontaneous micturition, utilizing all the extraneous aids, such as tidal irrigation, various bodily postions, compression of the bladder by the hands and abdominal muscles, warm enemas, etc. These measures usually fail, but the occasional success makes the effort worthwhile. After transurethral resection has been adequately performed nearly all patients can void with little or no residual urine, and the majority have good urinary control.

## SUMMARY AND CONCLUSIONS

Thirty-nine cases of neurogenic bladder treated by transurethral resection have been followed for periods ranging from 3 months to more than 3 years. The results in this and other series justify serious consideration of employing this procedure to re-establish useful bladder function when this function has been lost in adults as a result of a central nervous system lesion. The lesion level has no apparent influence upon the ultimate outcome after transurethral resection.

166 N. Bellevue at Poplar (F.M.J.)

74 North St., Pittsfield, Mass. (J.L.B.)

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## SIMPLE CYSTECTOMY AND SEGMENTAL RESECTION FOR CANCER OF THE BLADDER

HUGH J. JEWETT

*From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Md.*

The position that any type of treatment will ultimately occupy in the management of infiltrating cancer of the bladder will depend on two factors: its range of efficacy, and a comparison of this range with that of other procedures. The limitations of each method can be determined only after the tumors so treated have been rigidly classified in regard to their physical extent as well as their degree of cellular differentiation. The cellular appearance indicates roughly the speed of

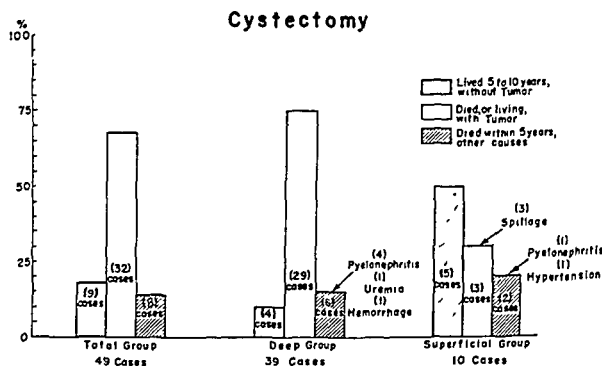


FIG. 1

the tumor. Its degree of infiltration, or extent, however, is governed by the combination of its speed and its age, and possibly also by the resistance of the host. Since the age of the tumor bears no constant relationship to the duration of symptoms it rarely is known with certainty, and any estimation of extent which is based on cellular appearance alone is apt to be unreliable.

Forty-nine patients with infiltrating cancer of the bladder were subjected to simple cystectomy prior to June 1, 1947 and survived operation (fig. 1). Nine (18 per cent) lived 5 to 10 years without evidence of tumor, but all have suffered renal damage of varying degree; 32 (65 per cent) died with cancer, and 8 (16 per cent) died within 5 years of conditions other than cancer. Each of these 8 patients, however, died of a urological complication. In 39 cases the tumor had infiltrated more than halfway through the muscularis of the bladder wall. Four of these patients (10 per cent) lived over 5 years without cancer; 29 (75 per cent) died with cancer, and 6 (15 per cent) died within 5 years of other causes. There were 10 cases in which infiltration had not reached the halfway level in the muscularis. Five of these patients (50 per cent) were free of tumor after 5 years, three (30 per cent) died of cancer, and 2 (20 per cent) died within 5 years of other causes.

Read at annual meeting, American Urological Association, Atlantic City, N. J., June 26, 1952.

The results in a comparable series of 46 cases of infiltrating cancer subjected to segmental resection prior to June 1, 1947 indicate that cystectomy may be preferable when the tumor is deeply infiltrating, but less efficacious when it is superficial (fig. 2). Four of 39 patients (10 per cent) with deeply infiltrating tumors were alive and apparently free of vesical cancer 5 years or longer after

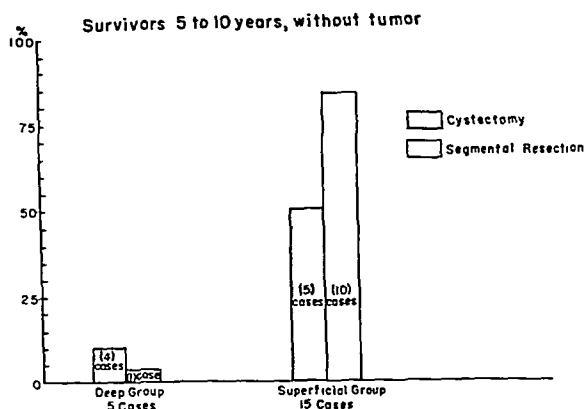


FIG. 2

TABLE 1. Deep group, 60 cases. Patients dying, or living, with tumors

|              | CYSTECTOMY         | SEGMENTAL RESECTION |
|--------------|--------------------|---------------------|
| Under 1 yr.  | 14                 | 15                  |
| 1-2 years    | 11                 | 12                  |
| 2-3 years    | 3                  | 4                   |
| 3-4 years .. | 1 (adenocarcinoma) | 0                   |
| Total        | 29                 | 31                  |

TABLE 2. Deeply infiltrating tumors

|                  | CYSTECTOMY  |                    |   | SEGMENTAL   |                    |
|------------------|-------------|--------------------|---|-------------|--------------------|
|                  | No of Cases | Histopathology     |   | No of Cases | Histopathology     |
| 5-year survivors | 4 (of 39)   | Mod diff. pap.     | 1 | 1 (of 34)   | Sl diff. pap. 1    |
|                  |             | Mod diff. epid.    | 2 |             |                    |
|                  |             | Undiff. ca         | 1 |             |                    |
|                  |             | Highly malignant 3 |   |             | Highly malignant 1 |

cystectomy, as compared with one of 34 patients (3 per cent) undergoing segmental resection. On the other hand, five of 10 patients (50 per cent) with superficially infiltrating tumors lived 5 years or longer without recurrence after cystectomy, as compared with ten of 12 patients (83 per cent) subjected to segmental resection. There are two reasons for the better survival rate in the latter group: Renal damage is less likely to ensue, and the possibility of implantation of cancer

cells is considered and guarded against to the extent of the operator's ability. Spillage is not usually anticipated in cystectomy, and therefore if a friable blad-

TABLE 3

| DEPTH OF INFILTRATION | LOCATION IN BLADDER | CYSTECTOMY               | SEGMENTAL RESECTION       |
|-----------------------|---------------------|--------------------------|---------------------------|
| Superficial           | Inferior part       | 9 (Highly malignant 3)   | 3 (All highly malignant)  |
|                       | Superior part       | 1 (Highly malignant)     | 9 (Highly malignant 3)    |
| Deep                  | Inferior part       | 29 (Highly malignant 20) | 12 (All highly malignant) |
|                       | Superior part       | 10 (Highly malignant 7)  | 22 (Highly malignant 21)  |

*Highly malignant*

Undifferentiated carcinoma

Slightly differentiated epidermoid

Moderately differentiated epidermoid

Slightly differentiated papillary (transitional cell)

TABLE 4. Superficially infiltrating tumors

| SERIES CLOSED<br>JUNE 1 | P.O. PERIOD OF<br>OBSERVATION | CYSTECTOMY  |                                     | SEGMENTAL   |                                     |
|-------------------------|-------------------------------|-------------|-------------------------------------|-------------|-------------------------------------|
|                         |                               | Total Cases | Survivors free of<br>bladder cancer | Total Cases | Survivors free of<br>bladder cancer |
|                         | <i>years</i>                  |             |                                     |             |                                     |
| 1947                    | 5                             | 10          | 5                                   | 12          | 10                                  |
| 1946                    | 6                             | 10          | 4                                   | 10          | 9                                   |
| 1945                    | 7                             | 8           | 3                                   | 9           | 8                                   |
| 1944                    | 8                             | 6           | 3                                   | 7           | 6                                   |
| 1943                    | 9                             | 4           | 2                                   | 5           | 4                                   |
| 1942                    | 10                            | 4           | 1                                   | 4           | 3                                   |
| 1941                    | 11                            | 1           | 0                                   | 3           | 2                                   |

TABLE 5. Superficially infiltrating tumors

| TABLE 5. <i>Superficially infiltrating tumors</i> |           |                  |                |              |                  |   |
|---------------------------------------------------|-----------|------------------|----------------|--------------|------------------|---|
|                                                   |           | CYSTECTOMY       |                | SEGMENTAL    |                  |   |
|                                                   |           | No. of Cases     | Histopathology | No. of Cases | Histopathology   |   |
| 5-year<br>sur-<br>vivors                          | 5 (of 10) | Well diff. pap.  | 1              | 10 (of 12)   | Well diff. pap.  | 1 |
|                                                   |           | Mod. diff. pap.  | 3              |              | Mod. diff. pap.  | 3 |
|                                                   |           | Sl. diff. pap.   | 1              |              | Sl. diff. pap.   | 1 |
|                                                   |           |                  |                |              | Mod. diff. epid. | 2 |
|                                                   |           |                  |                |              | Sl. diff. epid.  | 2 |
|                                                   |           | Highly malignant | 1              |              | Undiff. ca.      | 1 |
|                                                   |           |                  |                |              | Highly malignant | 6 |

der should be torn, or vesical contents expelled through the opened urethra at the prostatic apex, pelvic implantation of cancer cells may occur.

Of 60 patients with deeply infiltrating tumors who died with cancer, or who at the last report were known to have recurrence or metastasis, only one was believed to be free of recurrence for as long as 3 years (table 1). In the total

group of 73 deeply infiltrating tumors there were 5 patients who lived 5 years or longer without cancer; four following cystectomy, and one after segmental resection (table 2). Four of these 5 tumors were highly malignant.

In the cystectomy series 38 tumors involved the lower part of the bladder: base, trigone, vesical neck, as compared with 11 tumors occupying higher locations (table 3). In the segmental resection series this ratio was reversed, 15 tumors occurring in the lower part and thirty-one in the upper. Segmental resection in the case of a low-lying tumor usually requires re-implantation of one or both ureters and removal of all or part of the vesical neck when it is involved. Closure may be easily accomplished by anastomosing the widely mobilized vertex to the remains of the prostate.

In the total group of 22 patients with superficially infiltrating tumors treated either by cystectomy or segmental resection, some of the survivors have been observed over a period of 11 years (table 4). In the cystectomy series the survival rate remains at about 50 per cent each year after the fifth for as long as 9 years. The oldest survivor has lived  $10\frac{1}{2}$  years, apparently free of tumor but with considerable renal damage. The survival rate following segmental resection is much better, and 2 of 3 patients with infiltrating cancer are apparently well after 11 years. Furthermore, 6 of these 10 patients surviving segmental resection had highly malignant tumors (table 5). Resection, however, usually is not the procedure of choice when the tumor has a very large circumference or poorly defined margins, or when it lies close to the vesical orifice in the female. Multiplicity may be another contra-indication.

#### SUMMARY AND CONCLUSIONS

The results 5 years or longer after simple cystectomy in 49 cases of infiltrating cancer have been compared with those obtained by segmental resection in a similar group of 46 cases. Cystectomy provided a somewhat higher survival rate than segmental resection when the tumor was deeply infiltrating, and a somewhat lower survival rate when it was superficially infiltrating, regardless of its cellular appearance. Urological complications, usually renal, could be demonstrated in nearly all patients 5 years after uretero-intestinal anastomosis.

Proof of the superiority of radical cystectomy, with or without exenteration, will depend largely on the results 5 years or more after operation in cases with microscopic evidence of metastases in the lymph nodes.

## LOCAL ANESTHESIA IN THE MALE URETHRA

JOSEPH C. HAYWARD, LOUIS M. ORR AND HENRY F. LAGUETTE

Anesthesia of the male urethra, during cystoscopic examinations, is a problem with which every urologist is concerned. Numerous local anesthetic agents have been used and in most instances there has remained much room for improvement. Failure of sufficient anesthesia and untoward side reactions are the principal objections. It is the purpose of this brief article to present a method of local anesthesia in the male urethra during cystoscopic examination, which has proved most satisfactory over a period of years.

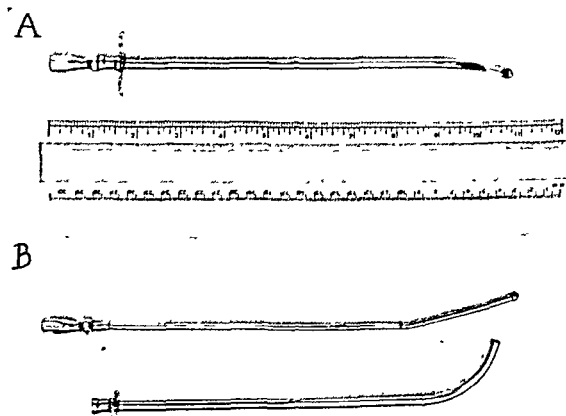


FIG. 1. Bransford-Lewis pill depositor introduced demonstrating tablets being properly placed in urethra.

Four per cent metycaine solution is instilled into the anterior urethra and allowed to remain 4 or 5 minutes, following which three  $\frac{1}{2}$  gr. metycaine tablets\* are placed in the posterior urethra and after a period of 3 to 5 minutes anesthesia of the entire urethra is realized. The tablets are placed in the posterior urethra by means of a Bransford-Lewis pill depositor (fig. 1) and care is taken to be sure that the tip of the instrument is well within the posterior urethra (fig. 2). The patient will still feel a sensation of pressure in the perineum on introduction of the cystoscope and the sensation is comparable to a numbness of the area involved, somewhat similar to that experienced in a spinal anesthesia. This subjective reaction to the anesthesia is possible as one of the authors experienced such an examination when this type of anesthetic was used.

During the past 6 years, only a rare untoward reaction has occurred; these were due to an apparent allergy to the 4 per cent metycaine solution instilled into the anterior urethra. On no occasion has instillation of the tablets in the posterior urethra precipitated undesirable reaction. We believe that the use of 4 per cent metycaine solution in the anterior urethra, followed by instillation of

Accepted for publication November 4, 1952.

\* These are prepared by Eli Lilly and Company, Indianapolis, Ind.

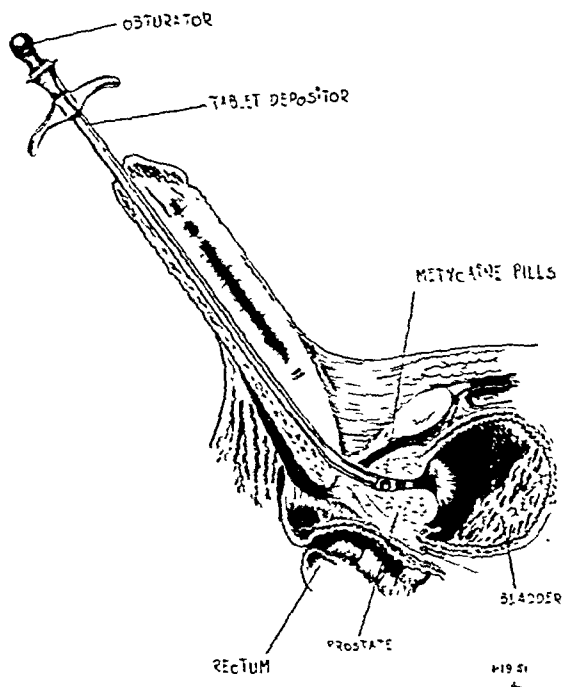


FIG. 2. Bransford-Lewis pill depositor

A—Assembled

B—Dissembled showing component parts.

metycaine tablets in the posterior urethra, is a safe effective means of securing anesthesia of the male urethra for cystoscopic examinations.

1107 Medico-Dental Bldg., San Diego 1, Calif. (J. C. H.)

1300 Kuhl Ave., Orlando, Fla. (L. M. O.)

34 Seventh St., Atlanta 5, Ga. (H. F. LaG.)



## PAINLESS DILATATION OF URETHRAL MEATAL STRICTURES FOLLOWING TRANSURETHRAL PROSTATIC RESECTION

RALPH R. LANDES

Despite liberal meatotomy, about every fifth patient who undergoes transurethral resection of the prostate is found to have a greater or lesser meatal stricture at the time of his first postoperative visit. Some of these are mild, soft and easily dilatable. Others are severe to the point of complete obstruction, indurated and resistant. Passage of sounds in the latter is extremely painful, and is not made less so by topical anesthetic agents. The pain is so intense that the patient is most loath to have the procedure repeated at proper intervals and the doctor is reluctant to carry the dilatation to the proper caliber and repeat it often enough to maintain it. Since meatal stricture is a very common cause of persistent post-resection pyuria and dysuria, it is most important to remedy it.

I have found it possible to make the procedure almost as completely painless as though it were done under general anesthesia by simply injecting from 2-3 cc of 2 per cent procaine through a fine hypodermic needle into the ventral angle of the meatus. The mucosa just inside of the meatus is pierced and the procaine is injected as the needle is advanced for two or three millimeters. No other points need be injected either because of the dispersal of the procaine or because of the distribution of the sensory nerves. After waiting about one minute the densest stricture can be dilated as far as one cares to carry it without the slightest discomfort to the patient.

The number of patients seen with meatal strictures who have had their prostates resected at distant clinics makes it pertinent to urge that such patients be informed of the need for postoperative urethral calibration.

*745 Main St., Danville, Va.*

Accepted for publication December 8, 1952.

# EFFECT OF AGE UPON GLUTAMINE SYNTHESIS AND GLUTAMINE AMIDE EXCHANGE OF RAT LIVER, KIDNEY AND TESTIS

JOHN M. REINER AND PERRY B. HUDSON

*From the Departments of Urology and of Biochemistry and the Institute of Cancer Research, College of Physicians and Surgeons, Columbia University, New York, N. Y.*

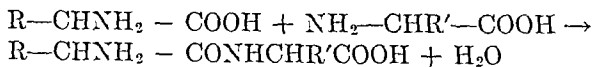
Investigations of cancer have quite reasonably included studies of tissue changes which occur with age. Within recent years, much of this effort has begun to center upon dynamic aspects—the enzymology and metabolism of the tissues at various ages.<sup>1</sup>

With few exceptions, the published work has dealt with catabolic enzymes.<sup>2</sup> This is perhaps due to the fact that much is known of catabolism, whereas little is yet understood of those enzymes which promote the synthesis rather than the breakdown of important organic substances.

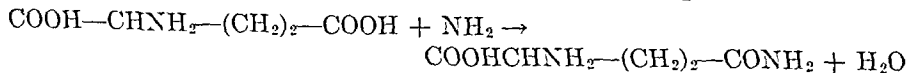
The present report is an initial survey of an attempt to detect alterations with age in the ability of rat tissues to synthesize glutamine and to promote glutamine exchange. This work, as well as similar studies still in progress, is based upon a simple hypothesis. It seems reasonable to assume that for a tissue to become cancerous it must manufacture more protein. In order to produce more protein, the enzymatic synthesis of protein by the tissue must be accelerated. Such increased enzymatic synthesis in cancer—or decreased with senescence—should be detectable by assays of the involved tissues.

This hypothesis has led to temporarily unanswerable questions. What, for example, are the important steps in protein synthesis by animal tissues, and how may they be measured? Although no definite answer to either question will be provided within the content of this report, the reasons for the selection of glutamine synthesis and amide exchange as indices of protein synthetic activity will be reviewed briefly.

Most investigators agree that proteins are synthesized from amino acids in a stepwise fashion. The fundamental reaction in protein synthesis is therefore probably the formation of the peptide link between two amino acids:



This may be compared to the equation for the synthesis of glutamine:



This reaction, described by Speck<sup>3</sup> and by Elliott,<sup>4</sup> is of particular interest because adenosine triphosphate (ATP) is required, and in fact enters stoichio-

This research was supported in part by a research grant (C-1639) from the National Cancer Institute, of the National Institutes of Health, Public Health Service.

Accepted for publication July 30, 1952.

<sup>1</sup> Cowdry, E.: *Problems of Ageing*. Baltimore: Williams & Wilkins, 1942.

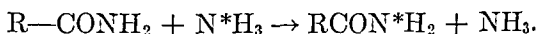
<sup>2</sup> Reiner, J. M.: *J. Gerontol.*, **2**: 315-320, 1947.

<sup>3</sup> Speck, J. F.: *J. Biol. Chem.*, **179**: 1405-1426, 1949.

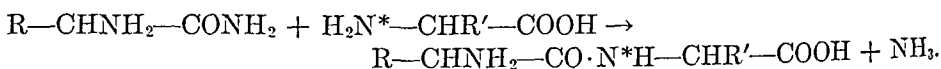
<sup>4</sup> Elliott, W. H.: *Nature*, **161**: 128, 1948.

metrically, so that one high-energy phosphate bond is consumed for every peptide bond formed. The participation of ATP increases the significance of the analogy between amide and peptide synthesis. The necessity for an energy supply for protein synthesis was made thermodynamically obvious by Borsook<sup>5</sup> and chemically obvious by numerous experiments on the incorporation of labelled amino acids into proteins.<sup>6</sup> In these investigations, 2,4-dinitrophenol, well known as an inhibitor of phosphorylation,<sup>7</sup> was found to inhibit protein synthesis. Parenthetically, it is of interest to note that the interesting properties of dinitrophenol were first demonstrated by Krahle and Clowes in studies on the inhibition of embryonic development,<sup>8</sup> and subsequently by Reiner<sup>9</sup> on adaptive enzyme formation.

Glutamine synthesis may be a model for the formation of all peptide bonds, as well as important in its own right. However, there is another reaction involving glutamine which illustrates a second interesting possibility. This reaction, discovered by Stumpf<sup>10</sup> and by Grossowicz et al.,<sup>11</sup> appears to involve the exchange of free ammonia for the amide grouping of glutamine. Thus, labelling the free nitrogen with an asterisk to clarify the exchange, the reaction may be written:



This may be compared with an attractive hypothesis for the mode of formation of the peptide bond in the synthesis of protein:



According to such an hypothesis, the key intermediate is the amide of an amino acid, which might be formed with the aid of high-energy phosphate in the same way that glutamine is formed. This idea is implicit in much recent work, but has not been very clearly formulated.<sup>12, 13, 14</sup>

#### MATERIALS AND METHODS

Because of their importance in the common parenchymatous degenerative diseases which are characteristic of senescence, the liver, kidney, and testis were selected for initial studies of activity in glutamine synthesis and amide exchange. White albino rats of the Sprague-Dawley strain were used. Normal rats of various ages were sacrificed by decapitation and the tissues were immediately removed and prepared for assay. Homogenates were made in a modification of the Potter-Elvehjem glass homogenizer using a tight-fitting lucite pestle. Five parts of 0.15

<sup>5</sup> Borsook, H. and Dubnoff, J. N.: *J. Biol. Chem.*, **132**: 307, 1940.

<sup>6</sup> Borsook, H., Deasy, C. L., Haagen-Smith, A. J., Keighley, G. and Lowy, P. H.: *J. Biol. Chem.*, **179**: 689-704, 1949.

<sup>7</sup> Loomis, W. F. and Lipmann, F.: *J. Biol. Chem.*, **173**: 807-808, 1948.

<sup>8</sup> Krahle, M. E. and Clowes, G. H. A.: *J. Gen. Physiol.*, **20**: 173-184, 1936.

<sup>9</sup> Reiner, J. M.: *Proc. Soc. Exp. Biol. Med.*, **63**: 81-84, 1946.

<sup>10</sup> Stumpf, P. K. and Loomis, W. D.: *Arch. Biochem.*, **25**: 451-453, 1950.

<sup>11</sup> Grossowicz, N., Wainfan, E., Borek, E. and Waelsch, H.: *J. Biol. Chem.*, **187**: 111-125, 1950.

<sup>12</sup> Johnston, R. B., Mycek, M. J. and Fruton, J. S.: *J. Biol. Chem.*, **185**: 629-641, 1950.

<sup>13</sup> Hanes, C. C., Hird, F. J. R. and Isherwood, F. A.: *Nature*, **166**: 288, 1950.

<sup>14</sup> Waley, S. G. and Watson, J.: *Nature*, **167**: 360, 1951.

M KCl containing 0.01 M potassium bicarbonate were added per gram wet weight of tissue. The period of homogenization was three minutes at about 4000 r.p.m.

From these homogenates, two types of preparation were made:

1) "Solubilized" homogenates: Our early experiments on glutamine synthesis with whole homogenates in these laboratories gave low levels of activity as compared to values obtained from extracts of acetone-dried preparations. It therefore seemed plausible to apply the method of Kun<sup>15</sup> for solubilizing mitochondria with the aid of butyl alcohol, on the supposition that the access of enzyme to substrate was being denied by structural factors still intact in the crude homogenate.

2) Ultracentrifugal supernatants: Subsequent experiments, the details of which will be given later in this communication, showed that all of the enzymatic activity remained in the supernatant after prolonged high-speed centrifugation of the original homogenates. Treatment of these active supernatants with butanol either decreased activity or produced no change, suggesting that the enhancement of enzymatic activity by the butanol treatment of the whole homogenate was due to denaturation of an inhibitor. Evidence of the presence of such an inhibitor will be presented.

The assays were performed according to Speck<sup>3</sup> and Stumpf,<sup>10</sup> using hydroxylamine instead of ammonia in order to take advantage of the convenience and sensitivity offered by the color reaction of ferric ions with hydroxamic acids.

A standard of acethydroxamic acid prepared from acetamide by the method of Lipmann was used.<sup>16</sup>

The incubation mixtures, usually containing 0.2 cc of the tissue preparations in a total volume of 2.0 cc, were maintained at 37°C for 30 minutes.

## RESULTS

The variations with age of enzymatic glutamine synthesis and glutamine exchange rates of rat liver, kidney, and testis are summarized in figs. 1 and 2. Each value on the graphs represents the arithmetic mean of results obtained in six different animals in the age group. The unit of activity utilized here is equal to 1 micromole of glutamine synthesized or exchanged per gram of fresh tissue per hour.

Comparison of butanol extracts (fig. 1) with ultracentrifugal extracts (fig. 2) indicates that the latter are superior in the case of liver, especially with the tissues of younger animals, and most markedly so in the synthesis of glutamine. More detailed studies on liver suggested some possible reasons for this result.

Fractionation of the rat liver homogenates by differential centrifugation was performed in a Spinco preparative ultracentrifuge\* using the type 40 rotor. All activity was recovered in the supernatant after centrifugation for 1 hour at 40,000 r.p.m. (105,000  $\times$  g). In most instances, activity was actually increased. Thus in one experiment, glutamine synthesis and exchange activities of 114

\* Specialized Instruments Corporation, Belmont, Calif.

<sup>15</sup> Kun, E.: *Proc. Soc. Exp. Biol. Med.*, 77: 441-445, 1951.

<sup>16</sup> Lipmann, F. and Tuttle, L. C.: *J. Biol. Chem.*, 159: 21, 1945.

and 244 units respectively in the homogenate rose to 130 and 300 units in the supernatant fraction.

This sort of result suggests that some inhibitory component in the homogenate was removed by the centrifugation. Graphic illustration of this phenomenon is afforded by an experiment in which activity was determined on the homogenate, on the supernatant resulting from 5 minutes centrifugation at 17,500 r.p.m.

### GLUTAMINE SYNTHESIS in RAT LIVER

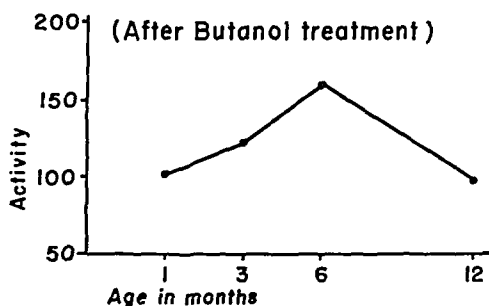


FIG. 1. Synthesis of glutamine in rat liver homogenates treated with *n*-butanol, in micromoles per hour per gram fresh weight of tissue. Conditions as described in text.

### GLUTAMINE SYNTHESIS in RAT KIDNEY (After Butanol treatment)

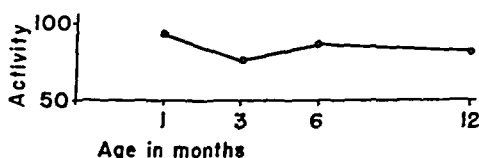


FIG. 2. Synthesis of glutamine in rat kidney homogenates treated with *n*-butanol, in micromoles per hour per gram fresh weight of tissue. Conditions as described in text.

TABLE 1. *Glutamine synthesis and exchange rates in centrifugal fractions of rat liver*

|                               | SYNTHESIS | EXCHANGE |
|-------------------------------|-----------|----------|
| Homogenate                    | 45        | 187      |
| First supernatant (20,000×g)  | 106       | 292      |
| Final supernatant (105,000×g) | 133       | 320      |

(Activity is expressed in micromoles of glutamine per hour per gram of fresh tissue.)

(20,000 × g), and on the supernatant from centrifugation at 40,000 r.p.m. (105,000 × g).

The first supernatant is presumably free of nuclei and mitochondria, but should contain the particles usually referred to as microsomes, while the final supernatant has been freed of these particulate elements. The data are summarized in table 1.

The variation of activity with amount of tissue is far from linear, which suggests that not all of the inhibitor has been removed even in the final supernatant. Such a result might also be observed with enzymes conforming to certain special

kinds of kinetics when not completely saturated with substrate. However, the latter explanation seems inapplicable to glutamine synthesis. All substrates except ATP are used at saturation values, and further increase of ATP concentration, while increasing overall activity, produced no increased tendency toward linearity in the dilution curve. Accordingly, another rough fractionation was carried out by isoelectric precipitation. The centrifugal supernatant was titrated with 2 per cent acetic acid while maintained at 0°C in an ice bath. The precipitates appearing at various intervals of decreasing pH values were collected by centrifugation in the cold (Ivan Sorvall Company, Model SS-1A, about 7000 r.p.m.

TABLE 2. *Glutamine synthesis and exchange rates in isoelectric precipitates*

| FRACTION                | CC OF FRACTION | SYNTHESIS | EXCHANGE |
|-------------------------|----------------|-----------|----------|
| Supernatant (105.000Xg) | 0.2            | 133       | 250      |
|                         | 0.1            | 80        | 211      |
|                         | 0.05           | 46        | 171      |
| pH 5.5                  | 0.2            | 11        | 59       |
|                         | 0.1            | 8         | 33       |
|                         | 0.05           | 6         | 18       |
| pH 5.0                  | 0.2            | 58        | 212      |
|                         | 0.1            | 29        | 135      |
|                         | 0.05           | 12        | 86       |
| pH 4.7                  | 0.2            | 13        | 57       |
|                         | 0.1            | 6         | 30       |
|                         | 0.05           | 1         | 18       |

TABLE 3. *Inhibition of glutamine synthesis by fractions of rat liver supernatant*

| FRACTION         | SYNTHESIS |
|------------------|-----------|
| pH 5.5           | 8         |
| 5.0              | 43        |
| 4.7              | 8         |
| 5.5 ÷ 5.0        | 30        |
| 4.7 ÷ 5.0        | 27        |
| 4.7* Supernatant | 45        |

\* This fraction is the final supernatant after the removal of all isoelectric precipitates.

for 5 minutes at 4°C). Each precipitate was redissolved in the initial volume of KCl-KHCO<sub>3</sub> used for the original homogenate. Table 2 presents a comparison of the dilution curves of a centrifugal fraction and three such precipitates prepared from it.

It is likely that the increased tendency toward linearity in the dilution curves results from this fractionation. This supposition was confirmed by recombining the fractions and demonstrating partial inhibition of the most active fraction by each of the others. A sample experiment is summarized in table 3.

Ultracentrifugal extracts of kidney and testis do not show the superiority to butanol extracts which was manifest in the case of liver. Preliminary experiments with the differential centrifugation technique suggests that the sharp fractiona-

tion found in liver does not occur in these tissues; activity is not confined to the ultracentrifugal supernatant (figs. 3-12). This may mean that the enzymes properly belong in one of the particulate fractions and are partially extracted during homogenization. Moreover, the possible involvement of unknown co-

### GLUTAMINE SYNTHESIS in RAT TESTIS

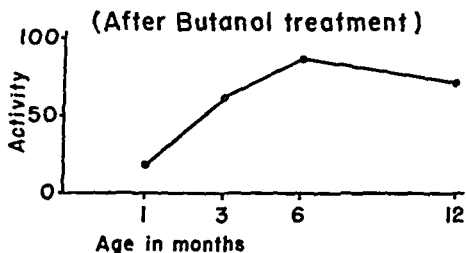


FIG. 3. Synthesis of glutamine in rat testis homogenates treated with n-butanol, in micromoles per hour per gram fresh weight of tissue. Conditions as described in text.

### GLUTAMINE EXCHANGE IN RAT LIVER

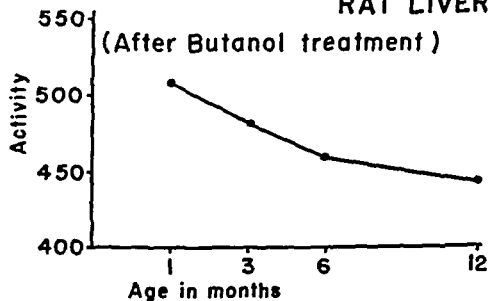


FIG. 4. Amide exchange of glutamine in rat liver homogenates treated with n-butanol, in micromoles per hour per gram fresh weight of tissue. Conditions as described in text.

### GLUTAMINE EXCHANGE IN RAT KIDNEY

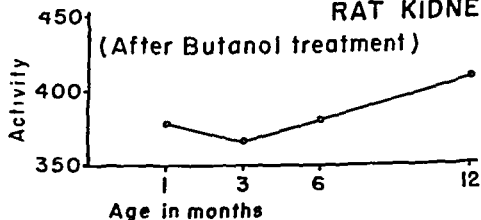


FIG. 5. Amide exchange of glutamine in rat kidney homogenates treated with n-butanol, in micromoles per hour per gram fresh weight of tissue. Conditions as described in text.

factors in these reactions has not been ruled out except for a few negative experiments with boiled juices in the case of liver; and the ultracentrifugal extracts in these tissues may be deficient in such factors. More intensive studies on the co-factor requirements of glutamine synthesis and exchange are now being conducted, using more highly purified enzyme preparations.

## GLUTAMINE EXCHANGE in RAT TESTIS

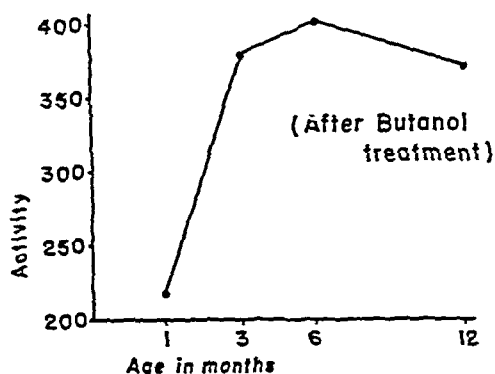


FIG. 6. Amide exchange of glutamine in rat testis homogenates treated with *n*-butanol. in micromoles per hour per gram fresh weight of tissue. Conditions as described in text.

## GLUTAMINE SYNTHESIS in RAT LIVER

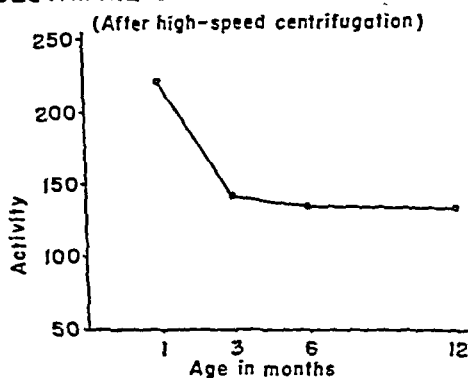


FIG. 7. Synthesis of glutamine in rat liver homogenates after centrifugation for one hour at 105,000 $\times$ g. in micromoles per hour per gram fresh weight of tissue. Conditions as described in text.

## GLUTAMINE SYNTHESIS in RAT KIDNEY

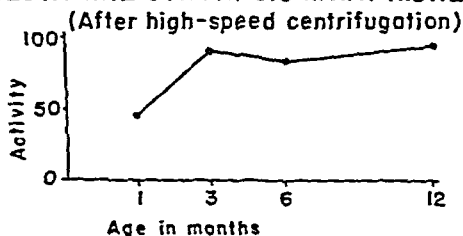


FIG. 8. Synthesis of glutamine in rat kidney homogenates after centrifugation for one hour at 105,000 $\times$ g. in micromoles per hour per gram fresh weight of tissue. Conditions as described in text.

## DISCUSSION

This report has dealt only with glutamine synthesis and amide exchange. It is admittedly exploratory in scope. For example, sufficient knowledge of the syn-



thesis of pentoses, nucleotides, and dinucleotides is now available to permit attempts at methods of assay for such enzymatic activities in animal tissues.

### GLUTAMINE SYNTHESIS in RAT TESTIS

(After high-speed centrifugation)

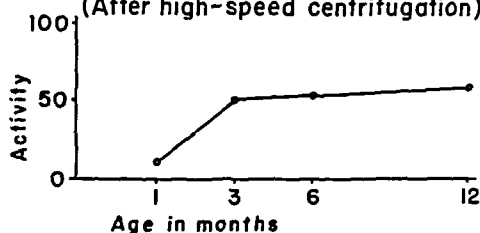


FIG. 9. Synthesis of glutamine in rat testis homogenates after centrifugation for one hour at 105,000xg, in micromoles per hour per gram fresh weight of tissue. Conditions as described in text.

### GLUTAMINE EXCHANGE in RAT LIVER

(After high-speed centrifugation)

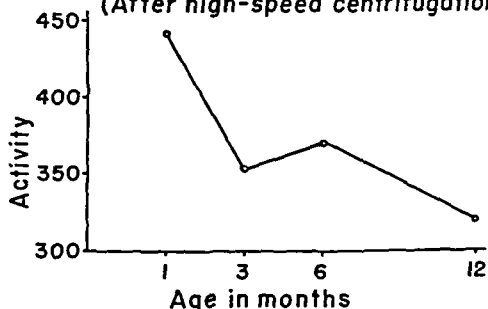


FIG. 10. Amide exchange of glutamine in rat liver homogenates after centrifugation for one hour at 105,000xg, in micromoles per hour per gram fresh weight of tissue. Conditions as described in text.

### GLUTAMINE EXCHANGE in RAT KIDNEY

(After high-speed centrifugation)

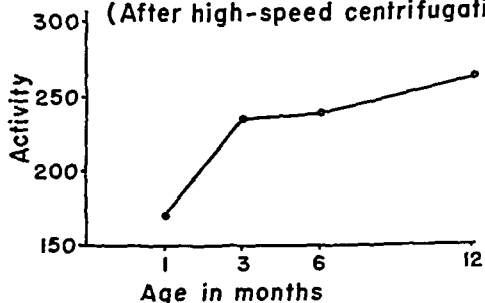


FIG. 11. Amide exchange of glutamine in rat kidney homogenates after centrifugation for one hour at 105,000xg, in micromoles per hour per gram fresh weight of tissue. Conditions as described in text.

The starting point in this investigation has therefore been selected, to a certain degree, arbitrarily.

The comparison between the different age groups has been made essentially

on a basis of tissue wet weights. In the case of rat liver the results would not be appreciably altered if they were based upon dry weight of tissue mass. However, it is obvious that enzymatic activity per cell would have greater physiological significance. In comparing normal with neoplastic tissues, such a basis for activity measurement would become mandatory. Desoxyribosenucleic acid content has been shown to be fairly constant for the diploid cells of an organism.<sup>17</sup> Accordingly, Davidson has proposed determination of DNA content for estimates of cell number in lieu of cumbersome cell count techniques.<sup>18</sup>

The demonstrated presence of one or more inhibitors of glutamine synthesis and amide exchange is suggestive of regulatory function, particularly since these inhibitors are apparently associated with some of the proteins of the tissues. Instances of similar inhibitory phenomena have been reported.<sup>19</sup> It is of course necessary to exclude inhibitions which are artifacts produced by the techniques

### GLUTAMINE EXCHANGE in RAT TESTIS

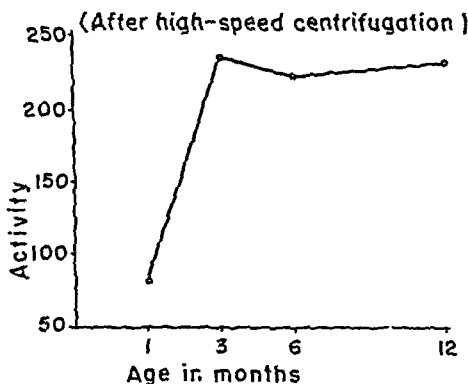


FIG. 12. Amide exchange of glutamine in rat testis homogenates after centrifugation for one hour at 105,000 $\times$ g. in micromoles per hour per gram fresh weight of tissue. Conditions as described in text.

used in preparation of the tissue. This can be accomplished by purification of the inhibitor and studies of its properties. Such studies are now underway.

Aging is obviously not the only physiological process which may affect rates of enzymatic synthesis. Prominent among the other likely regulators of such reactions are the endocrine glands. Hormonal depletion and administration experiments are now in progress.

Experiences with these enzyme systems have emphasized some problems in tissue enzyme assays in general. The requisites for a valid and useful assay have been discussed by Potter.<sup>20</sup> These include linear variation of enzyme activity with tissue dilution and with time. The results reported here illustrate the difficulty of establishing this more nearly ideal situation. Thus, when natural inhibitors are present in tissues, attempts at compensation for inhibition by using

<sup>17</sup> Swift, H. H.: *Physiological Zoology*, **23**: 169-198, 1950.

<sup>18</sup> Davidson, J. N. and Leslie, J.: *Nature*, **165**: 49, 1950.

<sup>19</sup> Zamenhof, S. and Chargaff, E.: *J. Biol. Chem.*, **180**: 727-740, 1949.

<sup>20</sup> Potter, V. R.: In *Advances in Enzymology*, **4**: 201-256, 1944.

high dilution of tissue may prove fruitless. Under such conditions fractionation designed to separate enzyme from inhibitor may succeed. It leads, however, to a preparation remote from the starting tissue material. Whether or not the active fraction then represents all of the enzyme activity initially present in the untreated tissue seems to be unanswerable. Such preparations may nevertheless prove useful on a purely comparative basis, provided all conditions of preparation and fractionation are carefully standardized.

#### SUMMARY

The variations with age in glutamine synthesis and amide exchange in certain tissues of the albino rat have been ascertained.

A natural inhibitor of these reactions has been encountered.

Limitations of the assay methods utilized have been delineated.

## THE UROLOGIC BATTLE INJURY IN THE KOREAN CONFLICT

H. B. HENKEL, CAPT. MC

Most of the literature dealing with problems of urologic battle injuries has been published with emphasis on statistics with little emphasis on pictorial representation. Because of the exigencies of the situation in this command, it has been a gratifying professional experience to have the opportunity to work with and observe these seriously wounded urologic patients. This conflict has produced just as severe types of urologic wounds as others and in about the same proportions. No personal credit is assumed for this work by me as many medical officers have all had their turn at treatment of many of these cases in their chain of evacuation. However, usually the definitive urologic surgery was done here or in the United States.

It is, therefore, the intention of this presentation to depict the various types of urologic wounds in a representative manner, rather than in a statistical sense; using well selected cases as typical of the areas involved and following their management from the time of initial trauma to their final disposition. No attempt has been made to compile endless statistics relative to the number of wounds of the kidney, ureter, bladder or genitalia. This was thought impracticable because of the lack of availability of accurate statistics. By specific examples which are a true picture of the over-all problems, an effort has been made to show how these problems were met in the most forward units, in the Mobile Army Surgical Hospitals (MASHs) and in the larger hospitals in the rear areas where the major definitive urologic surgery has been the predominating factor.

Seven classes of urologic injury have been arbitrarily selected as indicating the most useful classification with the degree of damage to the involved organ as the determining factor:

Class I. Wounds of the kidney.

Class II. Wounds of the kidney, ureter or adjacent viscera: renal combination wounds.

Class III. Wounds of the ureter.

Class IV. Wounds of the ureter and adjacent viscera: combined ureteral wounds.

Class V. Wounds of the bladder and/or adjacent viscera: bladder combination wounds.

Class VI. Wounds of the urethra and external genitalia.

Class VII. Wounds of the external genitalia with penetration into the adjacent viscera of the pelvis: combined genitalia wounds.

The majority of urologic injuries in combat are not simple injury to isolated organs. With the exception of the external genitalia, nature has hidden well

Read at annual meeting, American Urological Association, Atlantic City, N. J. June 25, 1952

Grateful appreciation is expressed to Mr. Hashimoto, medical artist of Tokyo University, whose excellent concept of the material and anatomic drawings made this paper possible. Also to Mr. Glenroy Stein, medical photographer of the 405 General Laboratory, Tokyo, Japan, for his photographic contributions.

within the confines of the body the other vital genito-urinary apparatus. The vast majority of urologic injuries are complicated by thoracic, abdominal or pelvic injuries. The latency in appearance of symptoms of urologic wounds is well known.

Much of the difficulty in the management of these wounds has been due to the extensive use of fragmentation missiles. In the earlier phases of the conflict there was a predominance of isolated missile wounds from small arms fire but in the later periods there has been a sharp increase in the numbers of those wounded from fragmentation of artillery and mortar shells. The extensive mutilation produced by high velocity fragments is well known and the degree of damage is directly dependent, not only on the size of the missile, but the speed with which it is driven through the tissue. It is this mutilation that presents the urologic surgeon with his most trying times.

Probably, more than any one factor, the rapid evacuation of the wounded has aided the surgeon in the maintaining of low mortality and morbidity statistics. The extensive use of the helicopter in this conflict has been a big stride forward in the procedures of evacuation since the days of World War II. All of the patients in these representative cases, received their initial surgery in the Mobile Army Surgical Hospitals within a few hours after initial trauma. It must be remembered that these wounded are in the younger age groups with bodies that are better conditioned to withstand the insult of trauma, hemorrhage and shock. In all probability it is the rapid evacuation; the extensive use of the antibiotics and the use of plasma and whole blood, in even the most forward units that is responsible for the saving of more lives than the surgeon's scalpel.

Each of these cases was selected as worthy of demonstrating problems as representative of their particular class of injury. They are by no means the sole representative of their class of injury but are multiplied many times in reality.

#### RENAL INJURY

In dealing with injuries to the kidney the question of the degree of damage is the paramount issue. An organ with the rich blood supply of the kidney and with its vital function, particularly when either is in jeopardy, must of a certainty be viewed with more than a jaundiced eye. Urography, either retrograde or excretory, is the only way short of actual exploration to determine serious renal damage. I have respect for the possibility of introducing infection from retrograde studies but prefer the method as the one of choice because of the availability of it; the clarity of the radiographs, the rapidity with which it can be done; the opportunity to inspect the lower urinary tract and the elimination of the possibility that the injured kidney may not be able to excrete the intravenous dye. Experience has taught that the calculated risk is less in favor of the development of infection than the disastrous results of unrecognized renal hemorrhage. Case 1 is an excellent example of the latency in appearance of urologic signs sufficient for investigation. Many times the condition of the wounded, at the time of the initial surgery, is so precarious that the replacement of blood loss and the checking of hemorrhage are all that can be done.

Case 1: This soldier was wounded by a .30 cal. bullet and flown by helicopter



FIG. 1. A. schematic representation showing course of bullet through ninth thoracic interspace on left in midaxillary line, penetrating left pleura, lung, dome of diaphragm, with rupture of spleen, left kidney and perforation of large bowel. In initial phase of injury, patient had left hemothorax with recognized rupture of spleen and unrecognized rupture of left kidney.

B. showing course of bullet through spleen with accompanying rupture of left kidney and perforation of large bowel in region of splenic flexure. Splenectomy was done in Korea. Rupture of left kidney was latent discovery and left nephrectomy was done 4 weeks following initial trauma. 50 cal. bullet was free in peritoneal cavity at initial laparotomy.



FIG. 2. Left retrograde pyelogram revealing rupture in middle of calyceal system with some extravasation. Film is poor technically, but there was obliteration of psoas shadow from massive left retroperitoneal hematoma. Right pyelogram was normal and function of right kidney was good.

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anatomic position of the ureter, access through a laparotomy incision is not always easy, especially when there is little suspicion of ureteral injury. Unless there is urinary drainage from a flank wound or free urine present in the peritoneal cavity at laparotomy, most of these cases are latent with their presentation of symptoms.

Case 2: This soldier was wounded by multiple .30 cal. bullets penetrating the abdomen. Initial surgery consisted of repair of the stomach with splenectomy and repair of the jejunum. Seven days later urinary drainage developed from the abdominal incision, and retrograde pyelography revealed extravasation in the upper one-third of the left ureter (figs. 3 and 4, A). Repair done over a splint-

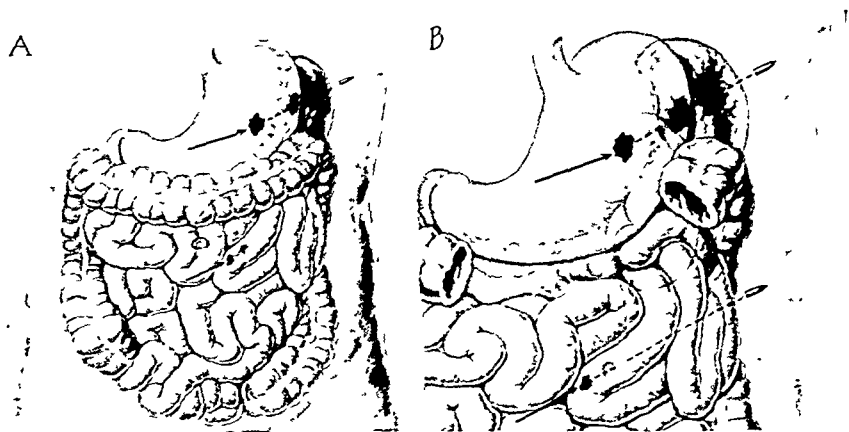


FIG. 3. A, schematic depiction of multiple penetrating wounds of abdomen. Through and through perforation of stomach; rupture of spleen; perforation of jejunum. Initial shock deep.

B, showing incomplete severance of upper third of left ureter which was unrecognized at time of initial surgery May 15, 1951. Injury to ureter due to bullet that previously had perforated jejunum.

ing ureterostomy tube was successful (fig. 4, B). Excretory urogram done three months after the repair shows little stenosis and good renal function. Ureteral injuries are among the most difficult to diagnose in the early stages when repair is most easily carried out; best results have been obtained when there was incomplete severance and when there was little elapsed time from the initial injury. Fortunately, ureteral injury alone is a rare condition. It usually accompanies serious damage to the surrounding viscera or the spinal column.

The usual picture is one, as described in case 2, where there is urinary drainage from the abdominal or flank incisions days after the initial surgery. If there is obstruction with secondary hydronephrosis, there may be chills with fever and the presence of a mass in the affected flank. In the early stages retrograde studies are imperative and if the defect in the ureter is determined to be partial, many times the use of an indwelling ureteral catheter will allow the area to heal. Usually retrograde studies are preceded by excretory urograms but all of the cases seen here have had retrograde studies prior to surgery. The length of



to a Mobile Army Surgical Hospital within 4 hours of initial injury. Laparotomy was done with repair of the bowel, splenectomy, left thoracentesis and a note was made that there was no serious damage to the left kidney (fig. 1, A, and B).

While preparing for the trip to the States, he went into shock and had gross hematuria; after the shock was combated, immediate pyelography was done. This film is poor but there was considerable left retroperitoneal hematoma (fig. 2). Immediate left nephrectomy was done and convalescence was uneventful. Retrograde studies were conclusive that serious damage existed. Had it been possible to do them earlier, perhaps within the first 24-48 hours of initial trauma, the kidney may have been repaired. Unfortunately, the condition of the patient precluded anything but the saving of life. Once such severe damage to a kidney has existed for days or weeks, all attempts to repair the organ with such severe laceration, as described here, are doomed.

The conservative management of renal injury has a definite role, especially when the injury is not of the penetrating variety but due to concussion, blows or crushing; but when there has been penetration of the abdominal, thoracic or retroperitoneal cavities, then conservatism has been supplanted by the need for immediate investigation which could mean exploration. I do not hold that, as has been stated many times, "renal exploration is tantamount to nephrectomy." Of course, the major concern in most of these cases is the immediate treatment of shock. Once this has been stabilized then, if there is extravasation of medium from without the confines of the calyceal or pelvic portions of a kidney, the possibility becomes more imminent that exploration is needed, particularly if there is indication of hemorrhage, which may not always appear as total gross hematuria. The degree of extravasation, its extent and the general clinical signs of the case, are the guideposts if exploration is needed. In any case, it would seem the wisest choice to err, if err it is, on the side of renal exploration early; at a time when the damage has a chance of being repaired without nephrectomy than to be forced into a piece-meal nephrectomy weeks later. Unfortunately, this has occurred too many times when the conservative measures are applied. Perhaps, in this respect, the time has come to make a firmer stand. Why, in the light of present day training, and with all of the drugs available, should the renal fossae be considered with so much taboo? The abdomen is certainly no stranger to well-meaning surgeons with much less indication than these problems present. In the battle injury, as opposed to those cases seen in civil practice, the predominance of penetrating wounds is far greater and it has been the experience here that the bleeding kidney with urinary extravasation is deserving of exploration.

#### URETERAL INJURY

As in cases of renal damage, the vast majority of ureteral wounds have accompanying damage to the adjacent viscera; in particular those of the peritoneal cavity, and those involving the vertebral column and spinal cord. There is no other group of cases among urologic injuries that presents as much difficulty in early diagnosis and has given such poor result with later surgery. Because of the

anatomic position of the ureter, access through a laparotomy incision is not always easy, especially when there is little suspicion of ureteral injury. Unless there is urinary drainage from a flank wound or free urine present in the peritoneal cavity at laparotomy, most of these cases are latent with their presentation of symptoms.

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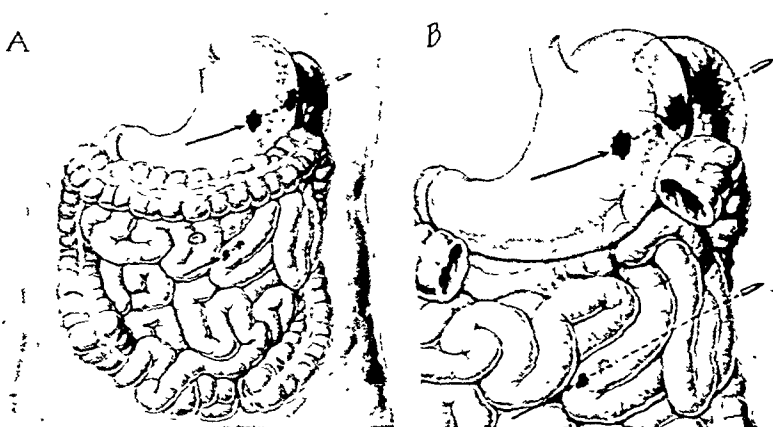


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elapsed time from the initial trauma to the time of discovery determines in large part the type of surgical procedure and its success. If it has been more than a few days, from the time of the initial wound to the time of discovery, then the chances of re-uniting the lumen of the ureter with proper healing taking place are poor indeed; particularly if there has been complete severance of the ureter. By this time, there is too much peri-ureteral reaction for proper healing. The ureter has a wonderful tendency to find itself but no tissue will heal properly with infection and necrotic tissue impeding the process. It is with partial separa-



FIG. 4. *A*, excretory urogram done May 22, 1951 revealing extravasation in upper third of left ureter with good function bilaterally. Retained bullet is present. *B*, excretory urogram done in October 1951 showing well healed anastomosis with good function.

tions or rents of the ureter that more success can be expected. Sometimes the insertion of an indwelling ureteral catheter from below will suffice; if not, then the defect can be repaired over an indwelling ureterostomy tube brought out through the pelvis of the kidney. The method of repair has been kept simple, using 000 or 00 chromic catgut and suturing the freshened margins in a transverse manner over an indwelling ureterostomy catheter that is brought to the outside through the flank, usually through the lower calyx, and an accompanying nephrostomy is done. The tubes are left in place usually from 4 to 6 weeks; this is at variance with some of the published data on the withdrawal of ureterostomy tubes but has given the best results for this area. In case 2 the ureterostomy tube was left for approximately 3 to 4 weeks when it slipped out; the end result in this case was gratifying. The postoperative dilatations of the ureter and the

leaving of the ureterostomy tube for prolonged periods of time are supposed to prevent as much as possible the formation of stricture. Whether a stricture develops or not depends not only on technique and the elimination of as much infection as possible, but to a considerable degree on fate. The results obtained from ureteral anastomosis in these cases are parallel to those usually attained with pyeloplasty. Fortunately, ureteral injury is uncommon, even in military urology, mainly because of its anatomical position, and when it does occur the mucosa has at least inherent propensities for regrowth but the healing in the muscular and adventitial layers is scar tissue per se, and therein is the crux of the thing.

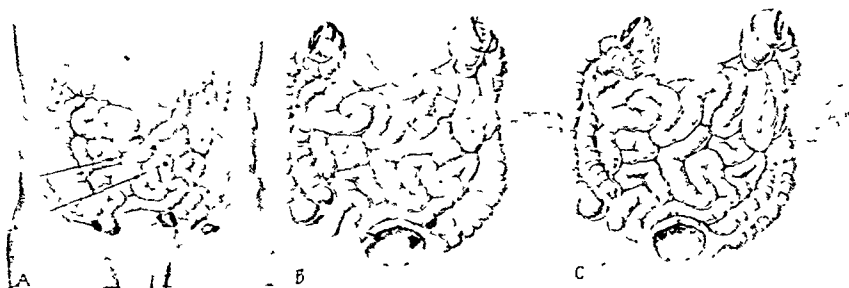


FIG. 5. A, schematic representation showing penetrating, multiple fragmentation wounds of abdomen involving small bowel, perforating bladder, and involving through and through perforation of sigmoid. Initial shock apparently not great. First treatment delayed 36 hours.

B, situation February 21, 1952, following transverse colostomy: Laparotomy revealed fistula between ileum, sigmoid and bladder with suprapubic fistula and small bowel obstruction at site of previous resection. Also ileosigmoid.

C, situation following surgery February 21, 1952. Fistula between bladder sigmoid and small bowel has been repaired. Resection of small bowel at site of obstruction and closure of ileosigmoid fistula. Bladder closed tightly suprapubically.

#### BLADDER INJURIES

Similar to those injuries of the kidney and ureter, bladder wounds are usually accompanied by trauma to the adjacent viscera, mainly the bowel and the great vessels of the pelvis. Their management is made somewhat easier by virtue of the early diagnosis and the surgical accessibility of the bladder. However, when complicated by fecal fistulas or hemorrhage from the vessels in the pelvis, as in case 3, they become problems of serious import.

Case 3: This soldier was struck with multiple penetrating fragments (fig. 5, A). Initial surgery was delayed 36 hours. In the Mobile Army Surgical Hospital laparotomy was done with an attempt at closure of the sigmoidal rent, and colostomy with repair of bladder. The largest fragment was left. There were three subsequent surgical procedures for secondary hemorrhage and 47 blood transfusions. The patient arrived at Tokyo Army Hospital with a fecal fistula suprapubically and small bowel obstruction (fig. 5, B). Bowel resection here with repair of entero-colic-vesical fistula (fig. 5, C; 6, A; and 6, B). Evacuated, ambulatory, to the States 5 months later (fig. 6, C).

Bladder injuries are usually of the combined type, as demonstrated here. In many cases the heavy antibiotic therapy has made possible the early closure of these fistulas.

elapsed time from the initial trauma to the time of discovery determines in large part the type of surgical procedure and its success. If it has been more than a few days, from the time of the initial wound to the time of discovery, then the chances of re-uniting the lumen of the ureter with proper healing taking place are poor indeed; particularly if there has been complete severance of the ureter. By this time, there is too much peri-ureteral reaction for proper healing. The ureter has a wonderful tendency to find itself but no tissue will heal properly with infection and necrotic tissue impeding the process. It is with partial separa-



FIG. 4. *A*, excretory urogram done May 22, 1951 revealing extravasation in upper third of left ureter with good function bilaterally. Retained bullet is present. *B*, excretory urogram done in October 1951 showing well healed anastomosis with good function

tions or rents of the ureter that more success can be expected. Sometimes the insertion of an indwelling ureteral catheter from below will suffice; if not, then the defect can be repaired over an indwelling ureterostomy tube brought out through the pelvis of the kidney. The method of repair has been kept simple, using 000 or 00 chromic catgut and suturing the freshened margins in a transverse manner over an indwelling ureterostomy catheter that is brought to the outside through the flank, usually through the lower calyx, and an accompanying nephrostomy is done. The tubes are left in place usually from 4 to 6 weeks, this is at variance with some of the published data on the withdrawal of ureterostomy tubes but has given the best results for this area. In case 2 the ureterostomy tube was left for approximately 3 to 4 weeks when it slipped out; the end result in this case was gratifying. The postoperative dilatations of the ureter and the

leaving of the ureterostomy tube for prolonged periods of time are supposed to prevent as much as possible the formation of stricture. Whether a stricture develops or not depends not only on technique and the elimination of as much infection as possible, but to a considerable degree on fate. The results obtained from ureteral anastomosis in these cases are parallel to those usually attained with pyeloplasty. Fortunately, ureteral injury is uncommon, even in military urology, mainly because of its anatomical position, and when it does occur the mucosa has at least inherent propensities for regrowth but the healing in the muscular and adventitial layers is scar tissue per se, and therein is the crux of the thing.

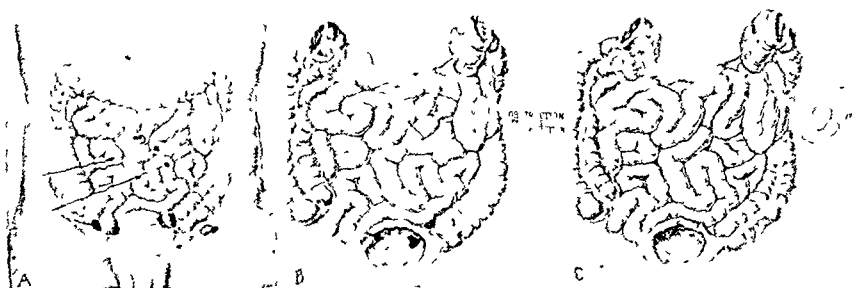


FIG. 5. A, schematic of abdomen with multiple penetrating wounds.

B, situation

after initial surgery. Fistula between bladder and sigmoid with suprapubic fistula and small bowel obstruction at site of previous resection. Also ileosigmoid.

C, situation following surgery February 21, 1952. Fistula between bladder sigmoid and small bowel has been repaired. Resection of small bowel at site of obstruction and closure of ileosigmoid fistula. Bladder closed tightly suprapubically.

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Bladder injuries are usually of the combined type, as demonstrated here. In many cases the heavy antibiotic therapy has made possible the early closure of these fistulas.

No case has been seen here where permanent diversion of the urinary stream was necessary. The bladder is a highly adaptable organ for plastic procedures; but the infection must be controlled or the repairs fail. Closure is desirable, early if possible, preferably at the time of initial trauma.

One factor that has encouraged the early repair of bladder wounds has been the extensive use of antibiotics. Repairs would not have been possible so early if large doses of penicillin, streptomycin and chloromycetin had not been begun at the time of initial injury. The suture line retained its integrity because infection had been kept to a minimum. Local application of dihydrostreptokinase has aided in preparing many fields that would have previously been "off limits" to any self-respecting surgeon. In one case maggots did a better preparation but not by professional intent.

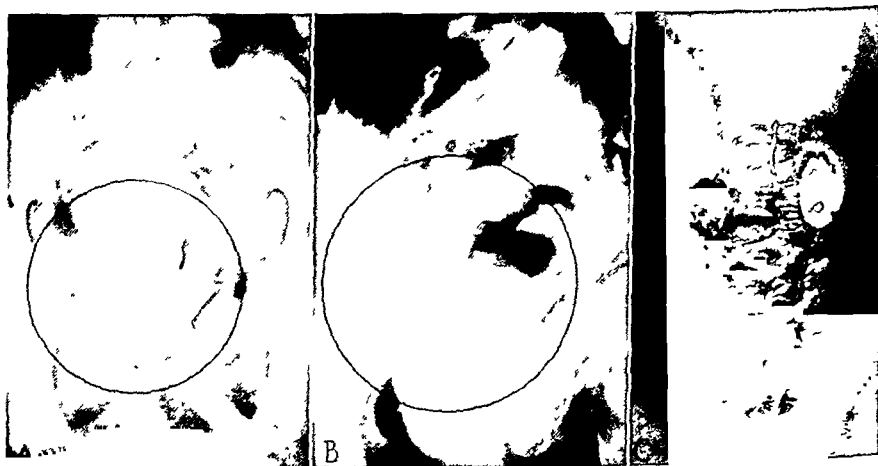


FIG. 6. *A*, barium enema revealing distortion of sigmoid with filling of bladder and evidence of some flow into ileum. *B*, left oblique film, as in *A*, showing passage of barium from sigmoid fistula into bladder. *C*, condition April 18, 1952 prior to evacuation to United States. Excellent urinary control with minimal infection. All wounds had healed; no more fecal or urinary drainage. Patient had gained 23 pounds, was ambulatory and had good appetite.

The position of the defect in the bladder is usually the determining factor as to the surgical approach and to the time of surgery. If there is possibility of repairing the damage at the onset of injury it is most desirable. While not as difficult to determine initially as those injuries of the kidney or ureter, again the general condition usually precludes the possibility of extensive reconstructive initial surgery. One patient, not reported in the representative cases, had multiple massive defects in the right side of the bladder with complete effacement of the vesical neck. There was complicating bowel damage but both ureters were intact. Five surgical procedures later, his vesical mucosa was intact. Because of the control of infection, as in case 3, these patients may be subjected to multiple procedures in attempts to re-establish the continuity of the bladder. Vesical calculi have not been a common complication in the postoperative period. The suprapubic catheters are removed as early as possible and constant urethral catheter suction is applied immediately in an attempt to heal the suprapubic wounds as

quickly as possible and ambulate the patients more rapidly. There have been four cases of periostitis pubis and symptomatic relief was obtained in three with deep x-ray therapy. Of interest is the observation that similar to those patients in the older age groups who have extensive procedures deep in the pelvis for rectal or bladder carcinoma, some of these men complain bitterly of impotence following surgery. This is especially true if the procedure has involved the bladder floor.

The neurogenic bladder is with us in this conflict, as it has been in others, as a complication of spinal cord injury. All patients with neurogenic vesical dysfunction are studied with cystometrograms, cystograms, cysto-urethrograms, cystoscopy and pyelography. Tidal drainage, as soon as possible, is instituted. The evacuation hospitals in Korea are equipped for this procedure, and it may be begun as early as 24-72 hours after injury. Previously it had been relegated as a rear echelon function. Initial suprapubic cystostomy has been used very infrequently and in those cases only where there is hemorrhage, massive infection or poor urethral catheter drainage or where there has been complicating bladder injury. Resection of the vesical neck is a procedure of benefit in well selected cases where there is definite hypertrophy and obstruction of the vesical neck; conditions which ordinarily do not develop until later in the course of the process and which seldom make their appearance while the patients are in this theatre. Early neurosurgical procedures have been done in an attempt to promote more efficient bladder emptying which is the desired end result in these cases. The result of these procedures are as yet inconclusive as insufficient time has passed to make any concrete observations; some of these procedures have increased the capacity of the bladder but the ability to empty is not markedly changed. The extensive use of the Stryker frame has made the physical care of the paraplegic easier, reduced the incidence of decubitus and improved the general condition. Partly because of the increased motion and probably due to the improved general metabolism there has been a low incidence of vesical and renal calculi. Bladder alkaline incrustations are frequent complications but these are removed cystoscopically when they occur. There have been few peri-urethral abscesses develop and none has produced a permanent urethral fistula. Practically all of these bladders show heavy pyuria and most have positive urine cultures but there have been few severe pan-urinary tract infections.

#### GENITALIA INJURIES

Wounds involving the penis, scrotum and its contents have been most common. Most of these wounds are due to fragmentation. Mutilating wounds of the genitalia require, as their prime requisite in management, a sound initial judgment. The importance of the external genitalia, both physically and psychologically, need not be emphasized. Radical procedures, unless absolutely necessary, are discouraged with the intent to save what is possible immediately and to reconstruct what is left at a later date.

Case 4: This soldier sustained complete avulsion of the testicles, partial amputation of the penis, rupture of the urethra, bladder perforation, and avulsion of the right thigh as a result of a land mine. Initial surgery in the Mobile Army Hospital was extensive débridement and control of hemorrhage (fig. 7). Repair



and skin grafting with perineal urethrostomy were done in Tokyo Army Hospital with good result (fig. 8). Wounds of the genitalia, fortunately, have not involved the pelvic viscera in the majority of the cases. Conservative measures are applied

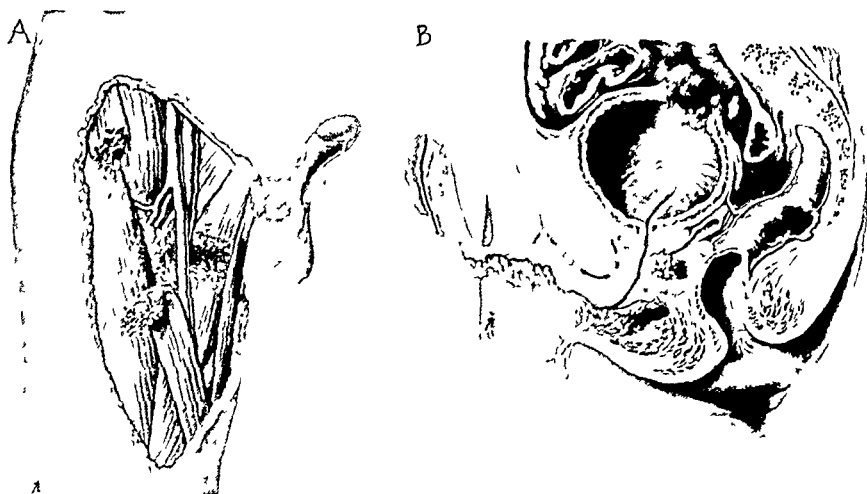


FIG. 7. A, appearance at time of original injury which was result of a land mine blast. Exposure of entire length of femoral vessels inferiorly to adductor canal with rupture of sanctorius and deep penetration of adductor group. Traumatic absence of right testicle with partial amputation of penis and total absence of left testicle. Accompanying deep penetration to pelvic viscera including damage to bladder, prostate, ileum, rectum and left seminal vesicle. Profound shock initially.

B, sagittal section to show penetration of fragments through urethra which was absent for distance of 4 inches into prostate and left seminal vesicle with penetrating fragment perforating dome of bladder and lying free in peritoneal cavity. Also perforation of rectum with perforation of ileum and small bowel fistula.

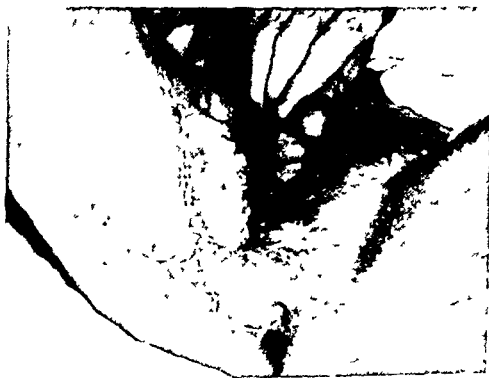


FIG. 8. Lithotomy view of healed right medial thigh wounds with skin grafts showing regrowth of scrotum and healed plastic procedure of penis. Perineal urethrostomy functioned well but required frequent dilatations. Status 3 months after initial wound and 6 weeks after skin graft.

where possible, and retained fragments have been left alone unless complications develop. The extensive mutilation produced makes the problem difficult.

In case 4, with the severe mutilation of his genitalia, this patient still has occasional nocturnal emissions from the perineal urethrostomy. While he retains marked chordee there is erectile function but coitus has been impossible. Sacrifice

of the testicles is discouraged unless the blood supply has been so impaired that viability is impossible. Many penetrating testicular wounds have been treated with only bed rest and support. If there was no secondary infection or severe intratesticular hemorrhage the retained fragments were left in place. When symptoms developed, the retained foreign bodies were removed. If there is the added trauma to the penis as in case 4 the end result is just short of total emasculation. Fortunately, these cases are rare.

As with the reconstructive work on other portions of the genito-urinary apparatus, the use of antibiotics has aided in doing early plastic procedures. When genital wounds are determined, search is made for accompanying injury to the pelvic viscera. The majority of wounds of the genitalia have not involved the pelvis or its contents but the possibility must always be considered; this is particularly to be suspected when there have been multiple fragments involved.

#### CONCLUSION

Four cases have been presented as representative of the type of genito-urinary injury encountered in the Korean conflict.

General principles have been stated concerning the management from the forward units to those in the rear echelons where the definitive urologic surgery has been the predominating factor.

*401 E. Capitol Ave., Springfield, Ill.*

## GENITAL SELF-MUTILATIONS BY MENTAL PATIENTS

LEON M. BEILIN

Genital auto-mutilations and/or injuries are not one of the more frequent patterns of psychotic behavior, though they are seen by most clinicians in mental hospitals and occasionally by urologists and general practitioners.

Such acts occur in most of the major psychoses, and also in neuroses and in organic brain diseases, such as encephalitis. Etiologically, there is no definite relationship between the phenomenon of self-aggression and the underlying mental disease; the self-aggression is merely a part of the symptom-complex.

The motives for this behavior and the methods used are often difficult to find or comprehend. The histories as given by the patients themselves may seem bizarre, vague, silly or humorous, but they are usually unreliable, as the motives are often disguised or concealed, more so by the neurotic patients, whose actions as a rule are more akin to those of the so-called true normals, than the psychotics, who, lacking inhibitions and with no loyalty to reality, make less effort at concealment.

Psychoanalysts claim that such individuals have an overpowering sense of guilt about their sexual sins, imaginary or real. The patient has the urge and attempts to do the obvious thing, namely, to rid himself of the guilty part of his body, his sex organs.<sup>1</sup>

It is not my intention, however, to speculate upon the psychodynamics of sexual deviations, but merely to indicate some of the more obvious patterns of psychotic behavior, as seen in the following cases. As a consultant urologist for state mental hospitals, I am primarily interested in the urological aspects of this problem. These cases were seen or treated by me at Manteno, Kankakee and Chicago State Hospitals and some in private practice, and they comprise a part of a larger series of similar cases, some previously presented.<sup>2</sup>

### CASE REPORTS

*Case 1.* C. H., a white man aged 72, married, 2 children, is a patient at Manteno State Hospital, with mental classification of "manic depressive psychosis, mixed type." For the past 30 years he was intermittently confined at various mental institutions, both public and private. He manifested psychotic behavior since early youth and made several attempts at suicide. There is now an ancient scar on his neck where he slashed his throat with a butcher knife.

In 1940, the patient had cut off his penis and scrotum and its contents with a pocket knife. Examination disclosed absence of external genitalia. A small urinary meatus at the puboscrotal area admitted a 20F sound. The patient voided in a sitting position and presented no urinary complaints, though his prostate, rectally, showed grade 2 enlargement.

Read in part at meeting of North Central Section, American Urological Association, Milwaukee, Wis., October 61, 1950; presented in the Scientific Exhibit, American Urological Association, May 21, 1951.

Accepted for publication May 28, 1952.

<sup>1</sup> Menninger, Karl. *Man Against Himself*. New York: Harcourt, Brace, 1938.

<sup>2</sup> Beilin, L. M. and Grueneberg, J.: *J. Urol.*, 59: 635, 1948.

According to the history, the patient, after some evasive answers, stated that the reason for self-emasculation was that his wife had refused to have intercourse with him. His wife, however, asserted that her husband was oversexed, was unfaithful, and, at the time of his mutilation, was having an affair with a married woman whose husband found him in *flagrante delicto* and threatened the patient to "cut his nuts off." This, presumably, had tended to develop a castration anxiety.



FIG 1. Case 1. Auto emasculation



FIG 2. Case 2. Auto-amputation of penis

ety on the part of the patient which led to the subsequent self-emasculation. At present, the patient is in good health, well-behaved and oriented, and apparently shows no regret for his act nor resentment toward his wife, who visits him frequently.

*Case 2.* C. F., a white man, aged 61, a Polish laborer, married, 3 children, has been at Chicago State Hospital since 1923, with mental classification of "dementia praecox, hebephrenic type." On June 26, 1947, when awakened by an attendant for the usual morning detail, he was found to be lying in his bed, literally in a pool of blood. Investigation disclosed that his penis had been ampu-

tated. Neither the amputated phallus nor the instrument that was used was ever found.

The patient was immediately taken to the emergency room and given first-aid by the night physician. Examination at this time showed that the penis had been completely and cleanly amputated up to the penoscrotal juncture. The patient was in shock, but there was no active hemorrhage, as the blood had already clotted. He was given the usual treatment for shock and loss of blood. Wet antiseptic dressings were applied locally and a Foley indwelling catheter was inserted transurethrally. Surgical repair was done about one week later, after which the wound healed, per primam. Subsequent urethral dilatations were followed to prevent a meatal stricture.

The patient is now voiding freely in the upright position, though the stream is splashing and his aim is poor. He is very negativistic, and no information was obtained from him as to the reason for or method of his injury. Later, however, he admitted to his wife that he used a pair of shears.

Subsequent investigation has disclosed that for the past 4 or 5 years the patient, when assigned to some labor detail, had invariably refused to comply with the order, saying, "I am a girl; it is too hard for a girl to do that." He also claimed that there had been a change in his body contour and that he was assuming the form of a woman. The patient has since discarded his given name of Carl and responds only to the name of Vicki.

*Case 3.* R. B., a 24-year old white man, with mental classification of "dementia praecox, catatonic type," had amputated his left testicle with a buckle of his overalls. Examination showed that the left half of the scrotum, testicle, epididymis, and the major part of the cord were completely torn away. The remaining part of the cord had retracted almost up to the external inguinal ring. Immediate surgical repair was done. The stump of the cord was ligated and the scrotum was closed with a mattress suture over a small Penrose drain. The usual chemotherapeutics, antibiotics and antitetanic serum were given. In spite of interference of the patient, the wound closed within three weeks.

While under pentothal sodium narcosis the patient maintained that the reason for his self-mutilation was fear of shock treatment which he was receiving at the time.

*Case 4.* L. S., aged 23, was recently admitted to Manteno State Hospital classified as "epilepsy with psychosis." One week previously he had amputated his right testicle with a butcher knife. The patient is a farmer and he had helped his father that morning to castrate some pigs and later, in the evening, he attempted to castrate himself, but succeeded in amputating only one testicle, as he was prevented from completing his intention by his mother, who happened to see blood on his clothing.

The physician who administered first-aid noted that the patient was quite calm and appeared to be in a state of inward exaltation. The patient was immediately taken to a local hospital, where he received the customary treatment for such injuries, including blood transfusions, antitetanic serum, antibiotics etc. The wound was clean and it was closed without drainage with no untoward effects, healing in about one week and leaving a heavy scar in the scrotum.

Past history showed that this patient had suffered from epilepsy since the age of 9 months, but these attacks were regarded by his family and school as fainting spells. But while in high-school, the patient himself, through intensive reading, had decided he had epilepsy. After this he became very depressed and antisocial, and developed religious identifications.

At the hospital, he stated that all his life people had been saying he was "nuts," and he concluded that if he took out his "nuts" he might be better off. However, when I asked the patient why he performed castration, he said, "I did not want to have epileptic children." \*

*Case 5.* C. L., a Negro aged 36, is a patient at Kankakee State Hospital with mental classification of "general paresis."

About three months previous to the time when first seen at urologic examination, he attempted to amputate his penis with a broken milk bottle. No reason for the act was given by the patient. Examination revealed a badly mutilated, fungating stump of the penis. When flaccid, it was about  $\frac{3}{4}$  of an inch in length,



FIG. 3. Case 5. Partial amputation of penis

wide in diameter, angry in appearance, and mostly free of the integument. Inguinal glands were enlarged bilaterally, indurated but not tender. Except for this mutilation, his general physical condition was good and he did not appear concerned about his predicament.

A biopsy of the stump showed inflammatory changes. Plastic surgery was not done, as the permission for such an operation was not granted by the patient's relatives.

*Case 6.* L. M., aged 26, was seen in consultation. Upon returning from military service, he had found that the girl to whom he had been engaged had married someone else. This was the precipitating factor in the development of acute schizophrenia. Shortly thereafter, he attempted to amputate his penis with a penknife, but succeeded only in cutting off the major part of the glans. It is well known that patients, at times, halt in the process of doing more extensive self-injuries because of shock, sight of blood, fear, etc. This patient was treated conservatively, and the injury had left a deformed but functionally useful organ.

\* Since this article was submitted for publication, this patient, on January 22, 1953, while still confined at this hospital, amputated the remaining testicle with a blade fashioned from a tin can, by which he incised the scrotum and severed the cord. He presented me with the corpus delicti with an air of final triumph.

This was typical psychotic behavior—self-punishment as revenge, which is symbolic in character.

Sexual self-mutilation may be considered as a form of masochism, even when, as it is occasionally, done by proxy, i.e., accomplished at the hands of another person. The next case may be placed in this category.

*Case 7.* W. W., a Negro aged 32, was seen in consultation in a private hospital. The reason for examination was a large, egg-shaped mass in the perineum. The patient stated that he had had it for about five years, that it had gradually increased in size and was now causing him some discomfort, especially on walking. He requested removal of this growth. On examination, the mass was found to be the size of a small gourd, soft, and freely movable. Two normal testes were palpated in the adjacent scrotum. Under infiltration anesthesia, the growth was easily extirpated.



FIG. 4. Case 7. Paraffinoma

The pathological report on the specimen showed that it was a paraffinoma. Confronted with this report, the patient at first disclaimed any knowledge of the source of this material, but later admitted that a "friend" injected it at his, the patient's request, into "the muscle of the penis," as a cure for impotence.

This patient was formerly a dental student and was acquainted with the use of paraffin in official surgery; and now he sought its injection into his penis by his friend whom he had instructed in the technique. Apparently, the friend's aim was bad, or the bore of the needle was too large, or the material used was too low in its melting point, but the paraffin had leaked into the perineum, where it had accumulated. This patient appeared to be of normal intelligence and obviously was homosexual.

*Case 8.* B. Z., aged 48, is a patient at the Chicago State Hospital, classified as "dementia praecox, catatonic." He has a compulsion to dig, scratch and otherwise injure his flesh, which he can not explain. He constantly thrusts pins, needles, tacks, bone fragments and other sharp objects into all parts of his body,

including the external genitals. His body is covered with scars of minor injuries, healed abscesses, etc. The external urethral meatus is scarred from a burn (cigarette).

Roentgenograms disclosed innumerable small needles and pins imbedded under the skin of almost the entire body, including the face. The patient admits inserting these needles; in fact, he does it openly in the presence of other patients.

This patient's self-destructive activities are probably of symbolic significance, as masochistic compulsion, in which all parts of the body become genitalized, or erotized.

*Case 9.\** L. W., aged 47, was seen in consultation. On the previous night, the patient had introduced into his urethra a curved glass violet-ray electrode, the modality commonly used by physiotherapists, beauticians, and others. In the process of onanistic manipulations, he broke this instrument at about midway of its shaft, so that, upon its withdrawal, he was able to retrieve only the distal



FIG. 5. Case 8. Needles in pelvis and external genitals

half, while the proximal part remained in situ in the posterior urethra. After his prolonged and vain effort to remove the retained part of the glass electrodes in the course of which the urethra was badly traumatized, he presented himself in the morning at the hospital in a state of almost complete collapse from urinary retention and profuse urethral bleeding.

I attempted to remove the rod transurethrally but failed. It was gripped tightly, as in a vise, by the swollen urethral mucosa and the strictured posterior urethra. In addition, this electrode was very brittle and would easily break off when grasped by forceps. External urethrotomy was done and the rod removed.

This man was a classical invert. At the age of 47, he was still a celibate and continent. He admitted his addiction to masturbation since early childhood and also to homosexual indulgences.

*Case 10.* D. C., aged 39, was admitted to the hospital with complaints of dysuria, dribbling, inability to empty the bladder and priapism, caused by a foreign body in the urethra. According to the patient's story, he had awakened

\* This and the following case were seen at the American Hospital, on the service of Dr. Max Thorek.



that morning from a drunken stupor to find himself in this predicament. He volunteered the information that on the previous night "a girl friend" had inserted a long crystal highball stirrer into his penis in order to produce a sustained erection.

On examination, a palpable rod was felt in the urethra, with the distal end firmly imbedded in the fossa novicularis. X-ray examination showed a foreign body occupying the entire length of the urethra and extending to the dome of the bladder.

Attempts to remove this glass rod transurethrally proved unsuccessful on account of marked swelling of urethral mucosa, persistence of priapism and the fear of further traumatization and the possibility of breaking the glass rod by manipulation. Anterior penile urethrotomy was not deemed advisable because this, as a rule, leads to the development of urinary fistula, which is difficult to



FIG. 6. Case 10. Crystal highball stirrer in urethra and bladder

heal. A suprapubic cystotomy was done and the rod removed. It measured 17 cm. in length, 1 cm. wide.

I believe this is one of the longest foreign bodies on record found in the urethra and bladder.

*Case 11.* H. O., aged 26, was admitted to the Alexian Brothers Hospital on the service of Dr. L. N. Wagner. The patient stated that on the previous night he had inserted a long pencil into the urethra, which slipped from his hand. In the attempt to remove it, somehow he broke the pencil and was unable to retrieve either part of it.

On examination, the abdomen was rigid and tender and in the perineum a long, pencil-like object was felt. A flat roentgenogram showed a small metallic shadow on the right side in the pelvis, apparently outside the bladder. Excretory urography showed evidence of intraperitoneal urinary extravasation. Immediate laparotomy was done, and about two quarts of urine was obtained through suction from the peritoneal cavity. The proximal part of the broken pencil, measuring about 5 cm., was found among the loops of the intestines. A small rent in the bladder on the posterior wall near the vertex was seen and closed by a purse-string suture. The peritoneal cavity was heavily sprinkled with sulfanilamide powder. The abdomen was closed without drainage.

At the same time, external perineal urethrotomy was done. It was found that one end of the distal portion of the pencil broke through the bulbous urethra and was lying parallel to it, and it was removed. A Foley catheter was inserted into the bladder through the external meatus and left indwelling for 9 days. By this time the patient's perineal and abdominal incisions were completely healed and he voided good stream through the external meatus. His prompt recovery was undoubtedly due, in a large part, to an early operation and liberal use of antibiotics.

#### SUMMARY

Eleven cases of genital self-mutilation in mental patients, a part of a larger series, some previously reported, are here presented. An attempt was made to integrate briefly some of their urologic and psychiatric aspects.

*185 N. Wabash Ave., Chicago, Ill.*

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### SECTION MEETINGS

*Mid-Atlantic Section*, Shoreham Hotel, Washington, D. C., April 22, 23 and 24, 1954  
*North Central Section*, Cincinnati, O., October 8-10, 1953  
*Southeastern Section*, Whitehall Hotel, Palm Beach, Fla., April 12-15, 1954

The members of the executive committees of the various Sections and the list of officers and members of the executive committees of the Branch Societies will be found on pp. 856-858, June 1953 issue

## METABOLIC STUDIES ON THE BILATERAL ADRENALECTOMY PATIENT

WILLIAM W. S. BUTLER, III, JOHN T. GRAYHACK, CHARLES L. RANSOM AND  
WILLIAM WALLACE SCOTT

*From the James Buchanan Brady Urological Institute, the Johns Hopkins Hospital,  
Baltimore, Md.*

The cure of prostatic cancer continues to be one of the major problems in Urology for numerous reasons: It is a common cancer, exceeded in the male only by cancer of the stomach and bowel; it makes few early symptoms, and hence diagnosis is usually made at a time when surgical removal is out of the question; in its disseminated form it leads to great suffering; its cause is unknown.

Initially, we wish to emphasize that early prostatic cancer is curable by total prostatectomy only, and that in spite of modern cancer tests, the principal resource in the diagnosis of early prostatic cancer is still the rectal examination.

Present methods of endocrine management of disseminated prostatic cancers which cannot be removed surgically began in 1939 with the work of Huggins and his associates at the University of Chicago. The simple theory on which endocrine therapy was based was formulated as a biological syllogism as follows: "In many instances a malignant prostatic tumor is an overgrowth of adult epithelial cells, as evidenced by their capacity to make acid phosphatase. All known types of adult prostatic epithelium undergo atrophy when androgenic hormones are greatly reduced in amount (by castration) or inactivated (by estrogen administration). Therefore significant improvement should occur in the clinical condition of patients with far advanced prostatic cancer subjected to castration or estrogen administration."

Since the work of Huggins and his associates hundreds of patients suffering from prostatic cancer have been treated either by surgical castration, estrogen administration or a combination of both. Pronounced improvement, sustained or unsustained, has been observed.

Early in this work it was recognized that many cases failed to respond or responded only for a short while to castration and/or estrogen therapy. Reasons for this were sought. Early it appeared that prognosis might be related to the size of the testes or to the type of prostatic cancer. There is little evidence to support either view. A study of the urinary 17-ketosteroids by Scott and Vermeulen suggested that following castration a reduction occurred followed by a rise to a level twice that observed prior to castration. This rise suggested an extragonadal source of 17-ketosteroids and androgens. This source was logically the adrenal. And so, in 1943 and 1944, Huggins and Scott<sup>1</sup> carried out a number of bilateral adrenalectomies in patients who had previously responded to castration or estrogen therapy but who had relapsed. The substitutional therapy used was suggested by Dr. George Thorn. This was before cortisone was available

Read at annual meeting, Mid-Atlantic Section American Urological Association, Philadelphia, Pa., May 5, 1952.

<sup>1</sup> Huggins, C. and Scott, W. W.: Ann. Surg. 122: 1031, 1945.

These studies suggested that some prostatic cancers were "androgen-independent." Because of the difficulty of maintaining the patient with no adrenals this work was dropped until recently when cortisone acetate became available in sufficient quantities.

Apparently Thorn, Harrison and Criscitiello<sup>2</sup> were the first to succeed in getting patients to live for any reasonable length of time following removal of both adrenals. Thorn had observed that 2 patients with hypertension became normotensive after developing Addison's disease and that one of these became hypertensive again following treatment of the Addison's disease with desoxycorticosterone acetate. Recognizing the benefit of a salt-free diet in hypertension and believing that following adrenalectomy it would be possible to manage individuals without DOCA or with minimal dosage, thus reducing the sodium retaining effect of DOCA, Thorn felt that bilateral adrenalectomy should relieve hypertension. During a ten month period prior to May 1951, these authors performed 13 bilateral adrenalectomies and showed that cortisone acetate was effective in maintaining life.

Subsequent to this Huggins and Bergenstal<sup>3</sup> reopened the issue of bilateral adrenalectomy in cases of relapse following castration and estrogen therapy for disseminated prostatic carcinoma. With the aid of cortisone and a certain regimen, they were able to keep alive patients with no adrenals. To our knowledge they have done some 35 to date, nine of which were for prostatic cancer. This work prompted us to re-examine the effect of bilateral adrenalectomy in cases of relapse, and today we wish to report the subjective and objective responses in two patients. We have primarily concerned ourselves with metabolic studies hoping to gain some insight into the mechanisms involved. We are certain that adrenalectomy is not a cure!

The first patient was a 56-year-old Negro who entered the Brady Urological Institute in October 1951 complaining of severe lumbar pain and difficulty urinating to the extent of frequency every hour and nocturia 6 times. He had been seen at another local hospital 8 months before where the diagnosis of carcinoma of the prostate had been made and bilateral orchiectomy performed. He noticed considerable improvement of the back pain during the first 3 months after castration but the symptoms gradually returned in spite of estrogen therapy. Examination revealed a lanky healthy Negro with a clear chest and no evidence of heart disease. Rectal examination revealed an extensive stony-hard induration of the prostate extending well into the right seminal vesicle and into the base of the left seminal vesicle. X-ray studies showed saturation metastases to the lumbar and pelvic regions.

On October 29, 1951 bilateral adrenalectomy was performed under gas, oxygen and ether anesthesia through separate flank incisions, removing the twelfth ribs. The blood pressure was easily maintained by the intravenous drip administration of 1-norepinephrine begun after the adrenal vein on the second side had been

<sup>2</sup> Thorn, G. W., Harrison, J. H., Criscitiello, M. G. and Frawley, T. F.: *Tr. A. Am. Physicians*, 64: 126, 1951.

<sup>3</sup> Huggins, C. and Bergenstal, D. M.: *J.A.M.A.*, 147: 101, 1951.

ligated. Review of the anesthesia chart shows the relatively smooth operative course and the ease with which it was possible to place the patient from left kidney to right kidney position. The blood pressure was maintained during the first 36 postoperative hours by continuing the intravenous drip of 1-norepinephrine. The drip was varied to maintain the pressure at 110 systolic. By the thirty-sixth hour there was a successful trial period without the pressor agent. The only abnormal cardiovascular sign during the administration of this agent was a transient pulse deficit. He was up on the third day and the postural hypotension was not enough to cause syncope, although the systolic pressure dropped to 90. Less distention was present than is usually seen in the nephrectomy patient. This patient was discharged from the hospital on oral cortisone, 12.5 mg. twice a day, on the forty-first postoperative day. He was free of lumbar pain during the immediate postoperative period and it has not returned during the period of observation, which is now over 5 months. He is alert, feels well and wants to return to his sedentary occupation. The rectal examination reveals thickening in the base of the prostate but it is no longer stony hard. The obstructive symptoms have disappeared and the urinary control is excellent. The blood and urine chemistries will be discussed with the second case.

The second patient was a 50-year-old Negro who was followed by the out-patient department for diabetes for 5 years. He was seen in the out-patient clinic in September 1950 because of severe lumbar pain. A plain urogram showed typical carcinoma of the prostate, metastases to the lumbar vertebrae. A pathological compression fracture of this region was found. In January 1951 a bilateral orchiectomy was performed. Despite castration and intensive estrogen therapy there was very little clinical improvement. When he was admitted in October 1951 he had lost weight from 148 pounds at the time of orchiectomy to 128 pounds at the time of adrenalectomy on November 1. On rectal examination the entire prostate and both seminal vesicles were stony hard.

On November 1, 1951, under gas, oxygen and ether anesthesia, bilateral adrenalectomy was performed through separate flank incisions through the beds of the twelfth ribs. The course was technically somewhat more difficult because of peri-aortic node involvement but both adrenals were completely removed. The adrenals showed a pasty yellow color instead of the golden brown color of the normal adrenal. The pressure was maintained as in case 1, with intravenous drip of norepinephrine. One thousand cubic centimeters of blood was given during the procedure. The postoperative course was fairly smooth but the intravenous pressor agent had to be continued for 48 hours. On the fourth day the patient was in a wheel chair. Pain was noticed radiating down the legs only on severe jarring or motion. Definite improvement was noted in the general well being of the patient during the first 2 months postoperatively but after this time he began to again require narcotics to sleep at night. Postoperatively no insulin was required to keep the fasting blood sugar in the normal range, and no glycosuria was detected.

To evaluate the effects of androgen on the adrenal-less patient intramuscular testosterone was given in January. Within 24 hours severe pain had returned

and an Addisonian crisis had been precipitated; the fever rose and the patient went into acute retention. The situation was controlled by increasing the cortisone dosage, catheter drainage, and intravenous glucose and saline.

Seven weeks later testosterone was again given and another episode of adrenocortical insufficiency ensued. Despite large doses of cortisone, fluids, glucose and saline the patient died on the 139th postoperative day. Autopsy was obtained and although the prostate appeared normal, every bone was involved and metastases were generalized. The metastases did not appear to be regressing.

An analysis of the blood and urine chemistries revealed the following facts. The nonprotein nitrogen in both cases remained within normal range both pre- and postoperatively. During the two episodes of adrenocortical insufficiency in the second case there was a slight elevation in the nonprotein nitrogen which

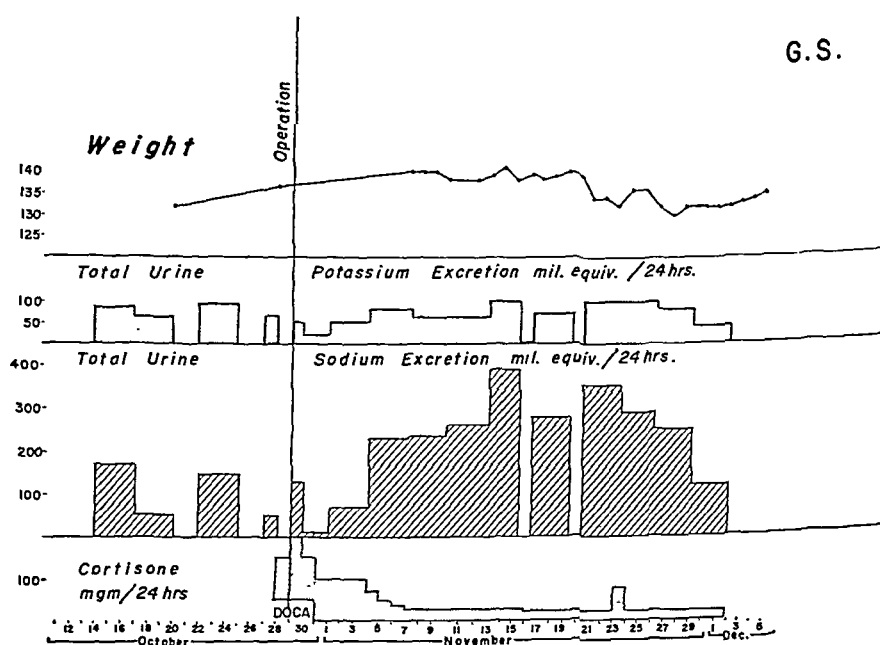


FIG. 1. Patient 1. Effect of therapy on weight and sodium and potassium excretion.

promptly subsided when supplementary cortisone was administered. This fact is considered one index that there was sufficient replacement with the amount of cortisone administered.

The blood electrolyte pattern remained normal pre- and postoperatively. The  $\text{CO}_2$  combining power, chlorides, and serum sodium and potassium were checked at frequent intervals and even though there was considerable edema and sodium retention in case 2 there was no interference with the acid base balance. Renal function by phenolsulfonphthalein test was unchanged in both cases.

Figures 1 and 2 show the total urine sodium and potassium excretion and the effect of cortisone and DOCA. It is obvious that sodium excretion is decreased more than necessary during the administration of DOCA. Also it can be seen that cortisone alone maintains the cation excretion within a normal range.

The second case shows the effect of testosterone on the sodium and potassium excretion, and the large amount of edema fluid that was retained, as evidenced by weight change.

The blood sugar of the first case was elevated but below threshold levels preoperatively, and glucose tolerance was definitely decreased. Postoperatively the patient showed a definite increase in glucose tolerance. In the second case the patient was a diabetic who required 15 units of protamine zinc insulin preoperatively. Postoperatively he had a decreased glucose tolerance but the insulin requirement dropped to zero. Also, during the episode of adrenocortical insufficiency, there was a lowering of serum glucose to shock levels.

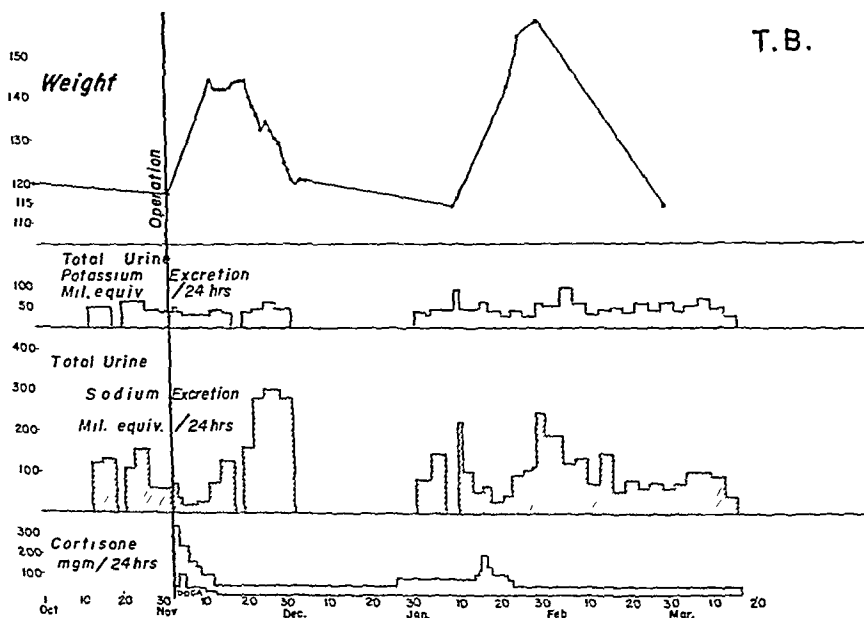


FIG. 2. Patient 2. Effect of therapy on weight and sodium and potassium excretion.

The 17-ketosteroids were studied by pooling three day urine specimens and running the determinations on aliquots (fig. 3). Both patients had normal range of ketosteroid excretion preoperatively and there was an increase during the immediate postoperative period apparently associated with cortisone and DOCA administration. During the first month there was a gradual decrease in the 17-ketosteroid output in both cases (fig. 4). The output varied in the second case during the episodes of adrenocortical insufficiency. During the period when the second patient was obviously becoming clinically worse the 17-ketosteroid output gradually increased, but the fluid intake and output did not follow any pattern and during the periods of diuresis there was increased 17-ketosteroid output.

The serum acid and alkaline phosphatase values decreased slowly in both patients following adrenalectomy. After the testosterone was given to the second patient there was sharp increase in both phosphatase values (figs. 5 and 6).



The serum uric acid and creatinine values were not changed pre- and post-operatively. The total urine creatinine and uric acid excretion remained at approximately the same levels pre- and postoperatively. However, during the time of operation when the DOCA was given and the large doses of cortisone were administered, there was increased excretion of both of these compounds.

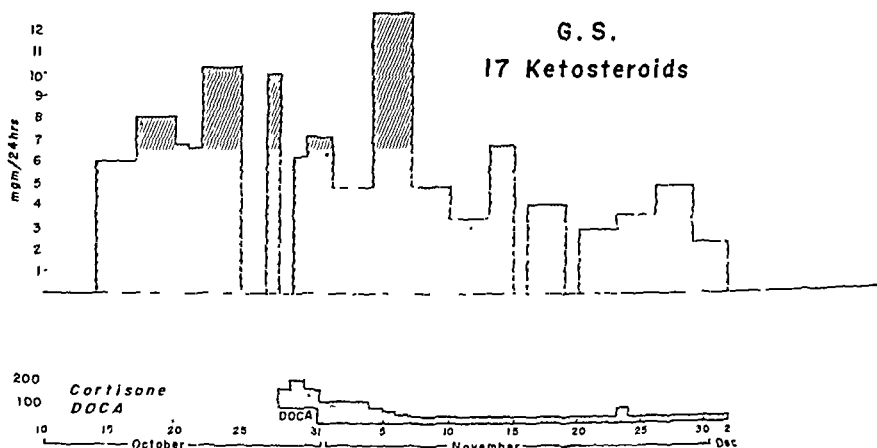


FIG. 3. Patient 1. Effect of therapy on 17-ketosteroid excretion. Blank space indicates determinations were not made.

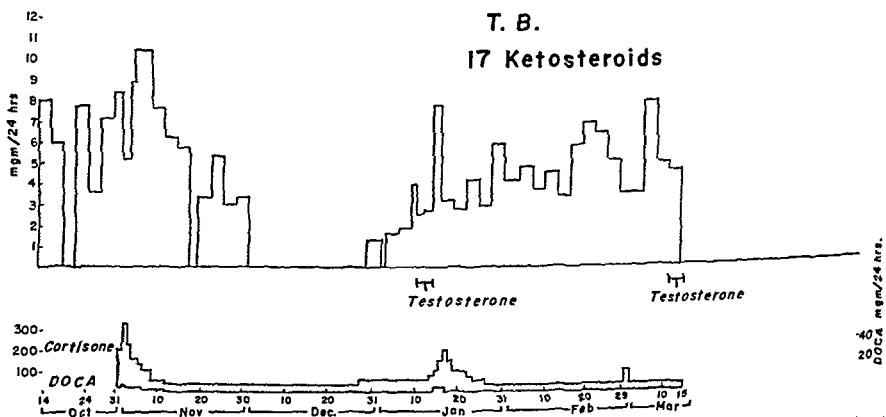


FIG. 4. Patient 2. Effect of therapy on 17-ketosteroid excretion. Blank space indicates determinations were not made.

There was no variation between the pre- and postoperative calcium and phosphorus serum levels. Inasmuch as the patients were not kept on low calcium diet the urinary excretion of these substances was not followed.

The eosinophil count dropped after ACTH intravenously in both cases before operation. Postoperatively there was an elevation far above the preoperative values and injection of ACTH failed to cause a lowering of the eosinophil counts.

The hemoglobin and total serum protein showed a definite improvement in the first case. Prior to operation hemoglobin values of 60 per cent and total serum protein at borderline edema levels were elevated by transfusions. After operation both of these values have increased without additional blood trans-

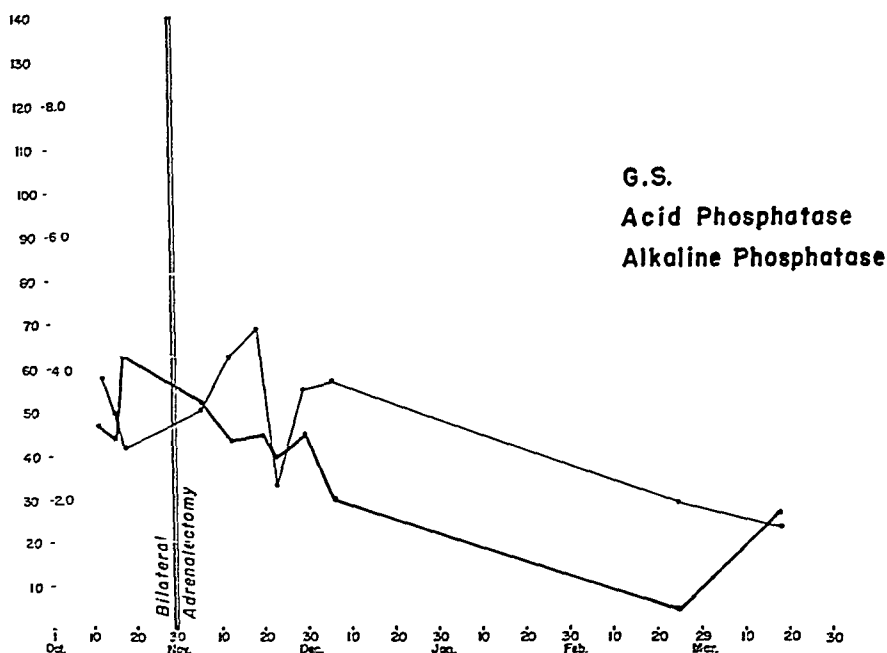


FIG. 5. Patient 1. Response of acid phosphatase (lower line, inner legend) and alkaline phosphatase (upper line, outer legend).

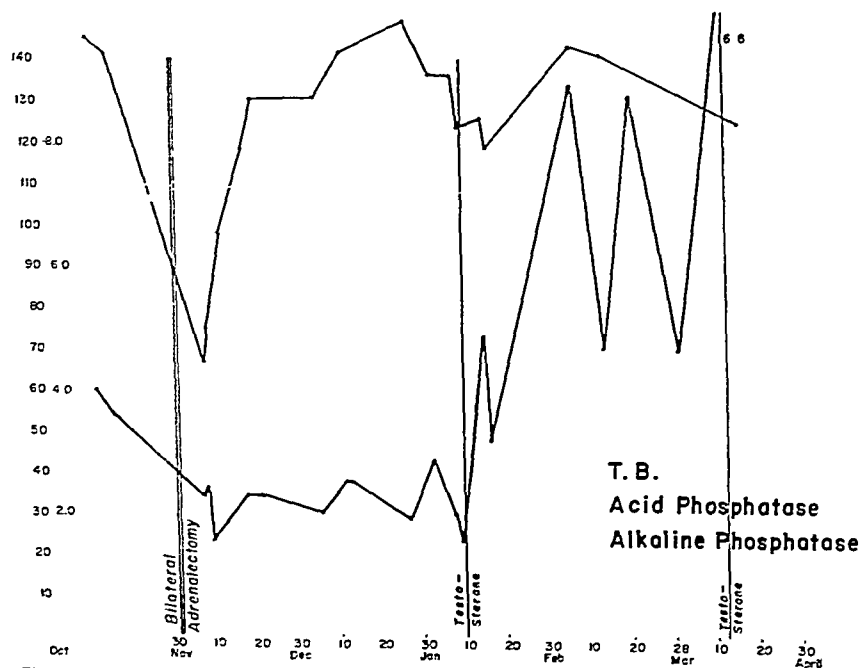


FIG. 6 Patient 2. Response of acid phosphatase (lower line, inner legend) and alkaline phosphatase (upper line, outer legend).

fusion and are now well within normal levels after 5 months. In the second case the anemia was severe enough to require transfusions every week to keep hemoglobin above 50 per cent before operation; during the second and third postoperative months he was able to maintain a value of 80 to 85 per cent without transfusions and the total serum protein was also maintained above 5.5 gm. per cent.

The basal metabolic rate showed a slight decrease in both cases 1 month after operation. The weight in the first case had increased from 132 to 156 pounds and this has paralleled his general improvement and clinical course. The second patient showed initial improvement and weight gain during the first 2 months but after this there was rapid fluctuation in the extracellular fluid volume and weight varied considerably.

### CONCLUSIONS

Bilateral adrenalectomy can be a safe and valuable procedure. It may prove to be of great value in the therapy of carcinoma of the prostate, hypertension and diabetes mellitus. Until the physiology of the adrenalectomized patient is better understood it must be restricted to the cases in the hopeless category.

Bilateral adrenalectomized patients may be maintained on 25 to 50 mg. of cortisone given orally each day in two doses. Acid base balance remains in equilibrium at this dosage when renal function is normal and the diet is adequate and contains 6 grams of sodium chloride. DOCA is not usually required to maintain these patients and even appears to be contraindicated by studies of total sodium and potassium excretion.

Glucose tolerance is increased after bilateral adrenalectomy when cortisone dosage is 25 mg. a day

Alkaline and acid phosphatases indicated improvement of two patients with carcinoma of the prostate with metastases after bilateral adrenalectomy. Another indication that there was a decrease in the cancer growth rate or metabolic rate was the ability of these patients to maintain total serum protein and hemoglobin values.

Testosterone increased the adrenocortical requirement and precipitated an Addisonian crisis twice in one of the patients without adrenals.

The 17-ketosteroid excretion decreased but never reached very low levels after adrenalectomy. In the second patient when the malignancy of the prostate became autonomous during the exacerbation there was an increase in the 17-ketosteroid excretion.

More fundamental studies are necessary to explain this.

## HISTOPATHOLOGICAL STUDY OF RENAL TUBULAR REACTION FOLLOWING INTRAVENOUS INFUSION OF HOMOLOGOUS HEMOGLOBIN SOLUTIONS IN DOGS

ALEX L. FINKLE

*From the Urology Division, Francis Delafield Hospital, Columbia University College of Physicians and Surgeons, New York, N. Y.*

Since 1940, intensified laboratory and clinical research has been carried out on the etiology and characteristics of the so-called lower nephron nephrosis.<sup>1</sup> Little progress has been made in illuminating the cause of the renal tubular epithelial injury induced by a host of seemingly unrelated "nephrotoxins" and involving selectively the distal segments of the ascending loop of Henle, as well as the distal convoluted and the collecting tubules. However, the histological picture of this damage has been nicely observed in dogs by Flink's serial biopsies of explanted kidneys.<sup>2</sup> Later publication of techniques for purification of canine hemoglobin<sup>3</sup> was adapted to the investigation of hemoglobin solution as a possible blood substitute in dogs.<sup>4</sup> In the latter study, renal clearance tests were performed, but the cytological changes in the kidney parenchyma attending excretion of the hemoglobin were not evaluated.

The present report represents incorporation of the refinements in production of hemoglobin solution with regular observations of the early development and temporal progression of the renal tubular lesions produced by intravenous infusion of known quantities of canine hemoglobin solution in dogs. This train of events is depicted from microscopical study of numerous biopsy specimens of explanted kidneys as well as of autopsy sections of the normally placed kidney.

### MATERIALS AND METHODS

Female mongrel dogs, about 13-18 kg. in body weight, were used for experimental transplantation of the left kidney to a subcutaneous site by the method of Corrigan and Pines.<sup>5</sup> "Veterinary nembutal" (Abbott) was given intravenously as an anesthetic agent in dosage of 30 [mg.]/kg. body weight. The operation was performed under sterile conditions. At the time of surgery the vaginal fourchet was enlarged, without sterile precautions, simply by incising the perineum longitudinally in the midline and everting the labiae with silk sutures. This brought the external urethral meatus into direct view and made for easy catheterization of the bladder.

Read at annual meeting, American Urological Association, Atlantic City, N. J., June 25, 1952.

Dr. Finkle's paper was awarded honorable mention by the Committee on Scientific Research, American Urological Association; Dr. Miley B. Wesson, chairman. *Editor*

<sup>1</sup> Lucké, B.: Lower nephron nephrosis. *Mil. Surg.*, 99: 371-396, 1946.

<sup>2</sup> Flink, E. B.: Blood transfusion studies III. The relationship of hemoglobinemia and of the pH of the urine to renal damage produced by injection of hemoglobin solutions into dog. *J. Lab. and Clin. Med.*, 32: 223-261, 1947.

<sup>3</sup> Hamilton, P. B., Farr, L. E., Hiller, A. and Van Slyke, D. D.: Preparation of hemoglobin solutions for intravenous infusion. *J. Exper. Med.*, 86: 455-463, 1947.

<sup>4</sup> Hamilton, P. B., Hiller, A. and Van Slyke, D. D.: Renal effects of hemoglobin infusions in dogs in hemorrhagic shock. *Ibid.*, 85: 477-487, 1947.

<sup>5</sup> Corrigan, F. P. and Pines, I.: Renal circulation after compression of the renal artery according to the method of Goldblatt. *Surg.*, 14: 88-98, 1943.

Donor dogs were subjected to phlebotomy, or dogs to be sacrificed for other purposes were exsanguinated by carotid cannulation as a source of hemoglobin. The method of Hamilton, Farr, Hiller and Van Slyke was employed for preparation of cell-free, sterile hemoglobin solution<sup>3</sup> modified only by the use of solid sodium bicarbonate for stromal precipitation, and then by dialysis of the hemoglobin solution in a cellophane bag against 0.85 per cent sodium chloride solution to constant volume. This accomplished concentration of the hemoglobin to 6-10 [gm.] per 100 cc solution, and reduced the volume of infusate necessary to achieve desired levels of circulating hemoglobin in the recipient animal.

Within 1-7 days after processing the donor blood—just before infusion into the experimental recipient—freedom of bacterial contamination was proved for each solution. Concurrently, oxyhemoglobin content of the infusate was measured colorimetrically and found to remain constant at 90-95 per cent during this period of refrigeration.<sup>6</sup> The alkalinity of the hemoglobin solution was carefully adjusted to pH 7.4 on a Beckman pH meter immediately prior to use, since a rise to as high as pH 8.0 was often found after storage of the final solution at 4°C for even 1 day.

From 15 to 120 days postoperatively, the surgically treated dogs, trained to lie quietly or tied loosely in the supine position, were given 500-1000 cc hemoglobin solution intravenously over a 2- to 4-hour period. In the animals surviving the procedure, biopsies of the explanted kidney were taken from 4 to 360 hours after completion of the infusion by means of a Silverman No. 14 gauge needle, following cleansing of the skin and under local 1 per cent novocaine anesthesia. Kidney sections were stained with hematoxylin and eosin. Similarly, tissue sections were prepared from both kidneys of those dogs which died, or were sacrificed at various intervals following the hemoglobin infusion.

All dogs were fasted and water was withheld for 24 hours prior to infusion of hemoglobin solution. For acidification of the urine (4 dogs) enteric-coated ammonium chloride was given orally in 3-gm. doses, at 18 hours, 12 hours and 1 hour before the infusion of hemoglobin.\* For alkalization of the urine (4 dogs) an aqueous solution containing 10 gm. sodium bicarbonate was administered by stomach tube 3 hours before starting the infusion of hemoglobin intravenously.\* "Hesperidin Methyl Chalcone," (Lilly) was given in 400 mg. doses, orally, at the same pre-infusion time intervals as was the ammonium chloride to some animals in each of the 3 groups of dogs, namely, the "acidified," "alkalinized" and "normal acid-base status."\*

<sup>6</sup> Evelyn, K. A. and Malloy, H. T.: Microdetermination of oxyhemoglobin, methemoglobin, and sulfhemoglobin in the single sample of blood. *J. Biol. Chem.*, **126**: 655-662, 1938.

\* Two dogs used in each of these experiments had not previously been given hemoglobin solution, whereas 2 animals of each group had 6 months earlier been so treated. Biopsy specimens of the explanted kidney taken several times during the 1-month period preceding the "acidification," "alkalinization," or "hesperidinization" experiments indicated morphological recovery in the kidney from the effects of the original experiment. Urea clearance values equivalent to pre-experimental levels demonstrated freedom from prolonged renal functional damage.

The acid and base alterations were arranged to evaluate influence of pII on extent of renal injury.

Hesperidin was given to test the anti-hemorrhagic effect ascribed to this drug, since Lucké<sup>7</sup> had described mechanical injury and parietal thrombi in veins near involved tubules in lower nephron nephrosis.

In 2 dogs, withdrawal of 25 per cent of the blood volume\* (roughly, 25-30 cc/kg. body weight) was carried out by venipuncture 4-5 hours preceding infusion of the hemoglobin solution. This crude equilibration of circulating fluid volume was attempted for the purpose of evaluating possible influence of the hemoglobin infusion upon extracellular fluid, upon the animal's general condition and upon the development of the renal lesion. This degree of hemorrhage was found to cause about a 15 per cent fall in urea clearance. The decrease in renal function was regained within 4 hours, without having affected appreciably the acid-base balance during the period of oligemia.

Crystalline hemoglobin solution prepared by the method of Cannan and Redish<sup>7</sup> was given in small doses, in solution, intravenously, to each of 2 dogs which had 6 months previously been subjected to infusion of hemoglobin solution and then to repeated biopsies of the explanted kidney. This infusion, consisting of 1 gm. crystalline hemoglobin in 25 cc of 0.85 per cent sodium chloride solution, was introduced daily for three 3-day periods, with intervening 2-day rest intervals between each of the 3 periods. A similar spacing regimen was carried out, using the same dose of standard hemoglobin solution, in 2 dogs, one of which had undergone "alkalinization" and the other "acidification" during hemoglobin infusion and renal biopsy experiments 6 months previously. This program was designed to reveal whether crystalline hemoglobin exerted an effect as deleterious as the crude hemoglobin solution, and also whether previous renal hemoglobinuric injury, recent or long-standing, constituted a "nephritic nidus" which predisposed to more rapid or more severe injury to the renal tubular epithelium.

Urine was collected during the first 4 hours following the intravenous hemoglobin infusion by an indwelling No. 18 Foley urethral catheter. Thereafter voided urine was recovered in breakers containing 25 cc toluol. Urine urea nitrogen was determined by the urease-aeration method of Van Slyke and Cullen<sup>8</sup> in the urea clearance tests.

#### RESULTS

A total of 24 hemoglobin solution infusions was given to 16 dogs. Four animals died within 3-18 hours after the infusion and one dog 34 hours later. One animal was sacrificed 1 hour following completion of an infusion. Of the spontaneous deaths within 24 hours, 2 animals were of the "normal acid-base status" and 1 each of the "acidified" and "alkalinized" groups, respectively. Two of these deaths could be ascribed to alkalosis, as reckoned from high serum bicarbonate and low plasma chloride levels secondary to laboratory error, namely, failure to measure and to correct the excessive alkalinity of the hemoglobin infusate. One dog, treated only with "Hesperidin" at the time of the hemoglobin infusion, succumbed to a respiratory infection 8 days afterwards.

Some 65 biopsies were taken from the explanted kidneys of 12 dogs under

\* Total blood volume was assumed to be 10 per cent of body weight.

<sup>7</sup> Cannan, R. K. and Redish, J.: *Blood Substitutes and Blood Transfusion*, edited by Mudd, S. and Thalheimer, W. Springfield, Ill.: Charles C. Thomas, 1942, pp. 148-151.

<sup>8</sup> Van Slyke, D. D. and Cullen, G. E.: A permanent preparation of urease, and its use in the determination of urea." *J. Biol. Chem.*, 19: 211-228, 1914.

various experimental conditions just defined. Fourteen of the animals came to necropsy post-experimentally, including those which died and those sacrificed at desired intervals.

*General observations.* None of the dogs was totally anuric, but diminished output of urine occurred in all surviving animals during the first day after the infusion of hemoglobin. Less than 100 cc of urine was found at post-mortem examination in the bladders of the 4 dogs which expired within 18 hours following the infusion. One dog (A-8) died 34 hours after infusion, having voided only 200 cc of grossly "bloody" urine in the post-infusion period; the bladder was contracted and empty at post-mortem examination. Ordinarily a normal urinary output or even a diuresis ensued within 24-48 hours after the experiment in the surviving dogs, and thereafter the daily urinary output remained within normal, pre-infusion limits. The urine was markedly blood-tinged for the initial 72-hour post-infusion period but then cleared gradually in all except 2 dogs of the "alkalinized" group, persisting in these up to about 110 hours; thereafter the urine remained wholly clear of erythrocyte-free hemoglobin.

There were no differences, biochemically or histologically appreciable, as to time of development of the renal tubular lesions, or to extent of parenchymal damage, or to rate of progression of the pathology between the "normal acid-base status," "acidified," "alkalinized," and "hesperidinized" animals given solutions of hemoglobin intravenously. Moreover, survival time of the animal, or rate and degree of recovery from the hemoglobinuric renal injury was apparently uninfluenced by these various pre-infusion treatments. Likewise, the quantities of hemoglobin infused in these experiments and the resulting levels of plasma hemoglobin seemed to bear no quantitative relationship to renal function, nor to type of renal tubular injury, nor to eventual epithelial recovery of the distal convoluted and collecting tubules. As expected, the large dosages of hemoglobin per kilogram body weight of the animal did impose an initially greater burden upon the kidney. This was reflected in generally but not invariably more pronounced depression of the renal clearance during the first 4-24 hours after infusion of the hemoglobin solution. However, this factor did not jeopardize recovery of these animals.

As noted previously, definite renal tubular epithelial injury resulted from a single infusion of hemoglobin solution, regardless of even low dosage of the pigment (fig. 2, A). But morphological and physiological recovery had ensued by the time secondary infusions were given to the same animal 5-6 months later. Even "irritative doses" of 1 gm. hemoglobin, given at frequent intervals, failed to produce a "nephritic focus" which would aggravate tubular epithelial pathology. Thus, relatively normal urea clearance values, as well as microscopic findings qualitatively resembling those of a single infusion of hemoglobin, occurred after multiple hemoglobinuric insults.

*Biochemical observations.* Details of renal function tests and of urinalyses were deleted from this communication. In brief, intravascular hemolysis followed infusion of hemoglobin solution in at least 3 experiments, but constant-rate excretion of plasma hemoglobin<sup>2,4</sup> was adequate; no deaths were ascribable to

this phenomenon. Regain of normal urea clearance values usually followed the phase of oliguria, namely, within 24 or up to 96 hours after the hemoglobin infusions. Alkaline urines developed within 96 hours in all types of experiments, proteinuria disappeared within 5-7 days and "formed elements" no longer appeared in the urinary sediment after 3-4 weeks. Blood urea nitrogen rose transiently for 1-2 days, but not above 25 mg. per 100 cc. Plasma electrolytes shifted slightly, without consistent patterns toward either acidosis or alkalosis. "Hesperidin" did not influence any of the biochemical or histopathological responses to intravenous infusions of hemoglobin.

*Pathological findings.* At autopsy, in spontaneous deaths or in animals sacrificed at desired intervals, the explanted kidney seemed grossly normal, except in 3 instances where it weighed 15-25 gm. less than the contralateral, hypertrophied organ. Figure 1 demonstrates an explanted kidney several months after surgery, shaved of overlying hair to illustrate the method of cleansing for biopsy and to enhance photographic detail.

The kidney appeared and felt turgid in those animals which died within 34 hours after infusion. The capsule stripped easily from the normally placed and



FIG. 1. External view of explanted kidney in subcutaneous left lumbar area. Dog A-1. Eight months after surgery.

the explanted kidney; occasionally, in the latter, infracapsular adhesions demarcated former biopsy sites. Bisection of the kidney revealed diffuse vascular congestion of cortex and medulla. The spleen was enlarged and congested in the early post-infusion deaths, but no other gross tissue abnormalities were noted. Large quantities of "sanguinous" peritoneal fluid, of hemoglobin content equal to the infusate, were found in the 18-hour deaths. In those animals sacrificed at 30- to 120-day intervals following hemoglobin infusion no remarkable gross pathology was detected.

In biopsy as well as autopsy sections of kidneys, the lesions detected microscopically were confined to the distal segments of Henle's loop, the distal convoluted tubules and the collecting tubules. Within as brief a period as 1 hour after the completion of the hemoglobin infusion, granular accretions and early crystalline-cast formation were observed in the lumina of these tubules (fig. 2, A and B). The epithelial cells of affected tubules suffered nuclear distortion and cytoplasmic vacuolization. As damage progressed with time, pressure necrosis of



these epithelial cells became evident (fig. 3, A). The destructive process was most pronounced within 24 hours, but onset of epithelial repair could be identified as early as 96 hours later, by which time hemoglobinuria had ceased in most cases.

A progressive loss in integrity of tubular casts was recognized by their fading eosinophilia and also by fragmentation with granulation (fig. 3, B). Damaged tubular cells, during reparative phases, appeared to separate from the basement membrane, and a few epithelial "ghost cells" were situated upon and/or within the disintegrating casts. A marked basophilia of the nuclei of newly forming

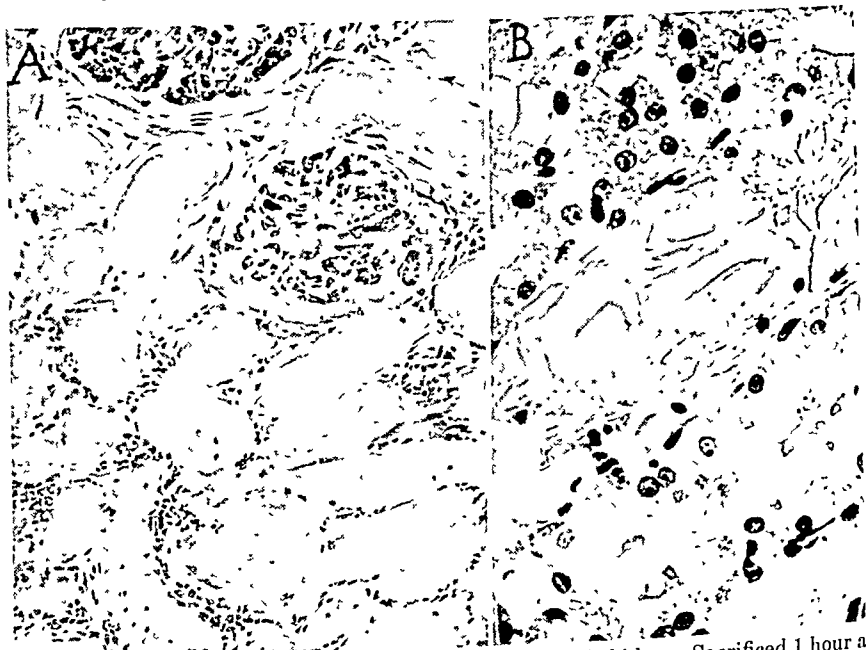


FIG. 2. A, slide 100B. Dog A-9. Autopsy specimen of left kidney. Sacrificed 1 hour after infusion of 30 gm. HGB in 600 cc solution, dose of 2 gm./kg. body weight. Distal segments of ascending loop of Henle, distal convoluted tubules and collecting tubules filled with granular material in initial stages of hemoglobin cast formation.  $\times 200$ . B, slide 115. Dog A-10. Autopsy specimen of right kidney. Death in alkalosis 3 hours after infusion of 10.7 gm. HGB in 150 cc solution of pH 8.5, dose of 1 gm./kg. body weight. Crystals of HGB in early stages of cast formation within distal convoluted tubule. Interstitial edema. Some post-mortem autolysis.  $\times 400$ .

tubular epithelial cells was observed: these cells appeared in small, circular clusters which, in this form, bore little resemblance to the usual tubular structure (fig. 3, B). By careful scrutiny, active mitosis of some nuclei could be observed at this point. Over a period of 10-12 days this regeneration of epithelial cells progressed until pre-experimental tubular morphology had been restored, presumably at the sites of damaged tubules. There were areas, doubtless traumatized by the biopsy needle, if not by the hemoglobin infusion, in which tubular damage had been so severe that connective tissue overgrew the former tubular site.

The glomeruli were free of injury. Most commonly there was no acute inflam



FIG 3 A slide 135 Dog A 3 Autopsy specimen of right kidney Death in alkalosis 8 hours after receiving 75 gm HGB in 600 cc solution of pH 8.0, dose of 3.5 gm/kg body weight Clear definition of hemoglobin casts, with evidence of pressure upon epithelium of affected tubules Negligible lymphocytic reaction in parenchyma B, slide 115J Dog A 15 Biopsy specimen of left kidney taken 141 hours after infusion of hemoglobin solution Pre infusion Hesperidin had been administered orally and then 24.9 gm HGB was given intravenously in 375 cc solution, dose of 2.2 gm/kg body weight Marked disintegration of intraluminal hemoglobin casts Small rings of deeply basophilic nuclei of new epithelial cells, presumably forming new tubules

matory reaction around either tubules or glomeruli. When such reaction was seen, the mobile cells were mainly lymphocytes, although a few leukocytes were occasionally present.

#### DISCUSSION

From the foregoing data it appears that hemoglobinuric injury to the lower segments of the nephron is paralleled by disturbance in function of the kidney. Although this renal dysfunction does not bear quantitative relationship to dosage of hemoglobin, no minimal critical level of plasma hemoglobin seems necessary; both large and small doses, within a range of 2-6 gm./kg. body weight, induce similar morphological and physiological damage. This finding is at odds with figures for an initial level of at least 3.7 gm. hemoglobin per 100 cc plasma, or an average for initial and 24-hour values of 2.2 gm. per 100 cc plasma, specified by Flink as requisite for the development of renal insufficiency in dogs.<sup>2</sup> The present study indicates that as little as 1 gm. hemoglobin given daily for 3 days produces microscopically identifiable injury in the lower nephron, even though renal functional reserve remains grossly unaltered, as manifested by normal urea clearance. Whether the difference between these and Flink's experiments, which otherwise present cognate results, can be reconciled by the fact that better-prepared hemoglobin solutions were used in the present study is as yet unknown. In any case, the linear rate of excretion of hemoglobin with time, to the extent of 25-50 per cent during the 8-hour period immediately following infusion of this pigment, suggests 2 conclusions, in light of these histopathological findings:

1) The initial burden imposed upon the excretory mechanism of the lower nephron by hemoglobin circulating freely in the plasma is not solely responsible for the development or extensiveness of the tubular epithelial damage.

2) The basis for renal malfunction is anatomical and is not simply a "transitory alteration in function."

The latter consideration provides support for the previously speculative comments by Hamilton et al. on this score.<sup>4</sup>

In a study of renal reaction to intraperitoneal injection of hemoglobin solution, Rather presents a photomicrograph depicting *intraglomerular* location of hemoglobin.<sup>9</sup> This finding was not encountered in the present study. Suitable explanation would have to invoke concepts of greater filtration of hemoglobin through "glomerular pores"<sup>10</sup> than could be absorbed, or the uncompensated injury to juxtamedullary glomeruli, involving operation of a "Trueta shunt."<sup>11, 12, 13</sup>

No therapeutic inferences applicable to man<sup>14, 15</sup> may be drawn from the

<sup>9</sup> Rather, L. J.: Renal athrocytosis and intracellular digestion of intraperitoneally injected hemoglobin in rats." J. Exper. Med., 87: 163-173, 1948.

<sup>10</sup> Yuile, C. L.: Hemoglobinuria. Physiol. Rev., 22: 19-31, 1942.

<sup>11</sup> Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J. and Prichard, M. L.: Studies of the Renal Circulation. Springfield, Ill.: C. C. Thomas, 1947.

<sup>12</sup> Goodwin, W. E., Sloan, R. D. and Scott, W. W.: The "Trueta" renal vascular "shunt." An experimental demonstration of neurovascular control of the renal circulation in the rabbit, cat, dog and monkey. J. Urol., 61: 1010-1027, 1949.

<sup>13</sup> Maxwell, M. H., Breed, E. S. and Smith, H. W.: Significance of the renal juxtamedullary circulation in man. Am. J. Med., 9: 216-228, 1950.

<sup>14</sup> Thorn, G. W.: Treatment of renal insufficiency. J. Urol., 59: 119-148, 1948.

<sup>15</sup> Merrill, J. P., Smith, S. III, Callahan, E. J. III, and Thorn G. W.: The use of an artificial kidney. II. Clinical experience. J. Clin. Invest., 29: 425-438, 1950.

present studies. Alkalinization did not seem to provide prophylaxis against damage to the lower nephron.<sup>16</sup> Investigations are being actively conducted to evaluate electrolyte balances in human renal lesions of this type<sup>17, 18</sup> and in cognate problems of renal function.<sup>19</sup>

Only conjecture as to the basic disease process resulting in "lower nephron nephrosis" can be advanced on the basis of the data in these experiments. When massive intravascular hemolysis occurs in man, either from trauma or other agents,<sup>1</sup> or from surgery,<sup>20, 21</sup> there are liberated into the circulation lipo-and-muco-proteins from the disrupted erythrocytic stroma. The presence in the plasma of these "foreign proteins" may sensitize the renal tubular epithelium. This factor, in conjunction with the deleterious effects of free hemoglobin *per se*, could jeopardize the potential recovery from the latter injury alone. Since no evidence is adduced in these experiments, nor in others known to the author, concerning an allergic effect upon tubular epithelium in this or other renal disease, this tenuous idea does not have any real significance in explaining the genesis of this disease.

Bing's contention that methemoglobin administration was a prerequisite to development of lower nephron disease<sup>22</sup> has been challenged elsewhere<sup>2, 4</sup> and was not borne out in the present study, in which oxyhemoglobin content of the infusate was high. "Hesperidin" had been reported to improve capillary fragility in the nephrotic patient,<sup>23</sup> but the sudden imposition of the renal insult in these animal experiments was probably too great to be combated by this questionably useful drug.

Dunn and Webster postulate that the process of *concentration* of hemoglobin in the lower nephron, secondary to reabsorption of the fluid vehicle at this site, determines cast formation in the lower nephron.<sup>24</sup> This reasoning appears more tenable than Bing's attributing this phenomenon to renal tubular anoxemia.<sup>22</sup> Based on the microscopical observations of the present study, it seems plausible that progressive dehydration of hemoglobin occurs as water is reabsorbed in the distal tubules, leaving there a hemoglobin cast. Tubular anoxemia may well result from the mechanical pressure exerted by the intraluminal casts, sufficiently compressing the epithelium to depress renal function. Even during this process, as urine is conveyed to the collecting tubule, some portions of casts would be

<sup>16</sup> Berry, N. E.: Anuria following blood transfusion. Report of two cases. *J. Urol.*, **58**: 239-243, 1947.

<sup>17</sup> Fox, C. L., Jr., McCune, D. J., Blakemore, A. H., Moloshok, R. E. and deLange, S.: The disappearance of edema through diuresis following artificial elevation of plasma sodium and bicarbonate. *Bull. N. Y. Acad. Med.*, **24**: 394-395, 1948.

<sup>18</sup> Fox, C. L.: Significance of electrolyte abnormalities in management of anuria, oliguria and edema. *Proc. Amer. Fed. Clin. Res.*, **5**: 23, 1949.

<sup>19</sup> Winfield, J. M., Fox, C. L., Jr. and Mersheimer, W. L.: Etiologic factors in postoperative salt retention and its prevention. *Ann. Surg.*, **134**: 626-634, 1951.

<sup>20</sup> Creevy, C. D.: The importance of hemolysis during transurethral prostatic resection: A clinical investigation. *J. Urol.*, **59**: 1217-1232, 1948.

<sup>21</sup> Creevy, C. D.: Mortality of transurethral prostatic resection. *J. Urol.*, **65**: 876-882, 1951.

<sup>22</sup> Bing, R. J.: The effect of hemoglobin and related pigments on renal functions of the normal and acidotic dog. *Bull. Johns Hopkins Hosp.*, **74**: 161-176, 1944.

<sup>23</sup> Thomas, W. A.: Nephritis and nephrosis. *Med. Clin. North America*, Chicago Number, pp. 134-141 (Jan.) 1947.

<sup>24</sup> Dunn, R. C. and Webster, S. H.: Hemoglobin crystals, casts and globules in the renal tubules of guinea pigs following chemical hemolysis. *Am. J. Path.*, **23**: 967-981, 1947.

swept along by the current and deposited there. Finally, these same hydrodynamic events involved in the deposition of casts in the lower nephron could explain the processes of discharge of such casts as tubular epithelial repair proceeded and more active urinary flow was reinstituted.

Intravenous infusion of 900 cc of fluid into a 15-kg. dog is comparable with administration to a 75-kg. man of 4500 cc of fluid. Stewart and Rourke<sup>25</sup> calculated from their observations in postoperative patients that an increase occurred in extracellular fluid up to 80 per cent of the volume administered within 3-4 days afterwards. Thus it is obvious that in the present experiments severe disturbances of fluid balance were imposed in addition to the deleterious influences of the hemoglobin itself. Relatively large amounts of hemoglobin-rich peritoneal fluid were found in those animals autopsied within the first 18 hours following intravenous infusion of hemoglobin in these experiments. This suggests that "an emergency peritoneal reservoir space" for both hemoglobin and excessive extracellular fluid may be utilized by the organism in an intensive effort to maintain homeostasis. Darrow and Yannet reported that their experimental increases in peritoneal fluid induced anuria.<sup>26</sup> Therefore, this feature of extracellular fluid imbalance demands consideration in explaining the oliguria observed during the first 24 hours after administration of hemoglobin solution intravenously in this study.

Debate as to the mechanism of anuria in the lower nephron syndrome is not concerned wholly with extrarenal factors, as may have been implied in the preceding paragraphs. While this point remains unsettled,<sup>27, 28</sup> various mechanisms, operating singly or together, such as decreased renal blood flow<sup>14, 29</sup> initiation of a "Trueta shunt"<sup>31</sup> and increased intrarenal pressure<sup>30</sup> merit theoretical interest.

Lastly, the absence of aggravated secondary injury to the lower nephron, following previous hemoglobinuric injury to the same animal, requires amplification. It might well be expected that a history of kidney disease would bring about a reduction of renal reserve. And by further rational extension, repetition of the same offense against the same animal 6 months later should cause a more severe renal dysfunction the second time. It is suggested that the present experiments, producing *acute* anatomical and physiological trauma, did not impede relatively complete renal recovery, within the limits of the dosages of hemoglobin given. This pathology of lower nephron nephrosis differs, for example, from an initial bacterial nephritis, a diffuse parenchymal disease, from which recovery

<sup>25</sup> Stewart, J. D. and Rourke, G. M.: The effects of large intravenous infusions on body fluid. *J. Clin. Invest.*, **21**: 197-205, 1942.

<sup>26</sup> Darrow, D. C. and Yannet, H.: The changes in the distribution of body water accompanying increase and decrease in extracellular electrolyte. *J. Clin. Invest.*, **14**: 266-275, 1935.

<sup>27</sup> Gaberman, P., Atlas, D. H., Kammerling, E. M., Ehrlich, L. and Isaacs, J.: Renal anoxia syndrome: A review and report of 22 cases. *Ann. Int. Med.*, **35**: 148-168, 1951.

<sup>28</sup> Peters, J. P.: The problem of cardiac edema. *Am. J. Med.*, **12**: 66-76, 1952.

<sup>29</sup> Houck, C. R.: Alterations in renal hemodynamics and function in separate kidneys during stimulation of renal artery nerves in dogs. *Am. J. Physiol.*, **167**: 523-530, 1951.

<sup>30</sup> Peters, J. T.: Oliguria due to increased intrarenal pressure. *Ann. Int. Med.*, **23**: 221-236, 1945.

could be incomplete. Therefore, later exacerbations of such nephritis would fall upon irreparably and extensively damaged areas within the kidney, leading ultimately to renal failure and uremia. The lack of knowledge regarding the selectivity of site of disease in lower nephron nephrosis applies also to the exact processes of recuperative activity in the present experiments.

#### SUMMARY AND CONCLUSIONS

Sixteen mongrel female dogs were subjected to surgical explantation of the left kidney to subcutaneous position in the lumbar flank. This procedure permitted repeated biopsies at desired intervals following the intravenous administration of a purified hemoglobin solution in 22 instances and of crystalline hemoglobin in 2 cases. Histopathological study of biopsy and autopsy specimens of the kidney and urea clearance determinations were used to follow the morphological and physiological response of the organism to the insult.

Cytoplasmic vacuolization and nuclear distortion of the epithelial cells of the ascending loop of Henle, of the distal convoluted tubules, and of the collecting tubules accompanied formation of granular accretions within affected lumina as early as 1 hour following intravenous administration of hemoglobin solution. By 3 hours after the infusion, definite crystalline configurations—"hemoglobin casts"—could be discerned within these tubular lumina. The glomeruli were unaffected, although sometimes a widening of the intraglomerular space was noted, along with generalized interstitial edema of the renal parenchyma. When inflammatory cellular response occurred at all, the mobile cells were predominantly lymphocytes.

The earliest phases of tubular epithelial repair were observed within 96 hours after infusion of the hemoglobin solution. This process consisted of mitosis of epithelial nuclei and marked basophilia of the cells. Disintegration of tubular casts commenced concurrently, and the breakdown of formed casts, a process of "granulation," appeared to recapitulate the formative aspects. Either new tubular epithelium formed at sites of damaged cells, or scar tissue replaced areas of severe renal parenchymal injury.

Oliguria developed during the first 24 hours subsequent to the intravenous infusion of hemoglobin in dosages of 2 to 6 gm./kg. body weight. Urea clearance depression during this period confirmed the renal hypofunction. Improvement to normal urea clearance values ensued within 144 hours after hemoglobinuric injury, thus preceding cytological repair by several days.

Development of lower nephron disease in dogs acidified by orally administered ammonium chloride, or alkalinized by sodium bicarbonate, likewise given orally, was identical, anatomically and functionally, with that just described. The same lesions occurred in 2 dogs given small dosages of crystalline hemoglobin and in 2 other dogs given equal "irritative dosages" of standard hemoglobin solution for three 3-day periods. The histopathology characteristically produced in these experiments was unaltered by pre-experimental administration of "He-peridin" (one of the so-called "vitamin P" components purported to counteract capillary fragility).

Disturbance in extracellular fluid following the intravenous administration of relatively massive quantities of fluid was manifested by free, "bloody" peritoneal fluid, in large volume, in those dogs succumbing within 3 to 34 hours after the infusion. In two experiments, pre-infusion bleeding of about 25 per cent of the circulating blood volume was performed. It was found that body fluid imbalance alone failed to account for type or extent of renal disease. In the discussion, speculations were proffered regarding fluid disequilibrium and intrarenal factors in the genesis of renal dysfunction.

Second experimental infusions of hemoglobin in the same dogs, as well as administration of small doses of both crystalline and crude hemoglobin 6 months after a primary infusion, resulted in lower nephron pathology identical with that originally observed in the given animal. This was interpreted to negate the existence of a "nephritic nidus" which would aggravate parenchymal damage attending later imposition of equally acute hemoglobinuric renal disease.

## THE HISTOLOGIC LESION OF CHOLEMIC NEPHROSIS

THOMAS W. HOLMES, JR.

*From the Department of Surgery, Alexander Blain Hospital, Detroit, Mich. and the Department of Pathology, Wayne County General Hospital, Eloise, Mich.*

Although there is no full agreement concerning the exact nature of renal lesions resulting from the excretion of abnormal concentrations of bile, most authorities localize these lesions to the tubular elements of the nephron, classifying them as degeneration of tubular epithelium, and bile stained casts occupying collecting and distal convoluted tubules. A variety of glomerular alterations have been mentioned, but none has been clearly incriminated in a significant series.

Recently, three isolated reports<sup>1, 2, 3</sup> have appeared, each describing unusual changes in glomerular histology, characterized by hypertrophy and hyperplasia of epithelium lining Bowman's capsule. In each instance there was extensive metastatic carcinomatosis of liver, and in one case jaundice was described. None of these authors attributed the observed changes to excreted bile, although such a potentiality was surely present.

In a study of kidney sections from a series of 68 autopsied individuals with jaundice, usually obstructive in type, hypertrophy and hyperplasia of glomerular capsular epithelium was observed in 73.5 per cent of cases, involving from 3 per cent to 30 per cent of glomeruli in each section, and tending to vary directly with the duration and intensity of icterus. The affected epithelial cells exhibited marked increase in cytoplasm, and enlarged nuclei situated near the center of the cell, rather than their position on the basement membrane, as is classically seen in cells enlarged by cloudy swelling. There was obviously hyperplasia as well as hypertrophy, since in the normal glomerulus only an occasional flattened nucleus can be seen about the capsular membrane.

These lesions appeared to be advanced degrees of a similar change involving tubular epithelium, in many glomeruli the enlarged cells seeming to invaginate through the tubular aperture into the capsular space (fig. 1). In cases with more prolonged or intensive jaundice, these hypertrophic cells tended to partially or completely encircle the parietal layer of the capsule, in an increasing per cent of glomeruli (fig. 2). In no case was alteration of the visceral layer of Bowman's capsule observed.

Other lesions included the classical bile stained casts, and a pink staining acellular exudate within tubules and glomerular spaces, which was thought to be the source of hyaline casts occupying tubules in the distal nephron.

Abridgement of a thesis submitted to the faculty of the Graduate School, Wayne University College of Medicine, Detroit, Michigan, in partial fulfillment of the requirements for the Degree of Master of Science in the Department of Surgery.

Accepted for publication July 28, 1952.

<sup>1</sup> Chappell, R. H., and Phillips, J. R.: Adenomatoid changes of glomerular capsular epithelium associated with adrenal tumor. *Arch. Path.*, 49: 70, 1950.

<sup>2</sup> Eisen, Herman: Adenomatoid transformation of the glomerular capsular epithelium. *Am. J. Path.*, 22: 597, 1946.

<sup>3</sup> Handler, F. P. and Saxton, J. A.: Hyperplasia of epithelium of renal tubules and glomerular capsules. *Am. J. Clin. Path.*, 20: 1121, 1950.



Glomerular capsular lesions were not observed in autopsy material from a comparable unjaundiced group.

In an effort to reproduce these lesions in the kidneys of healthy laboratory animals, obstructive jaundice was created in a series of rats by ligation of the common bile duct. Twenty-six male adult albino rats were used, ranging in

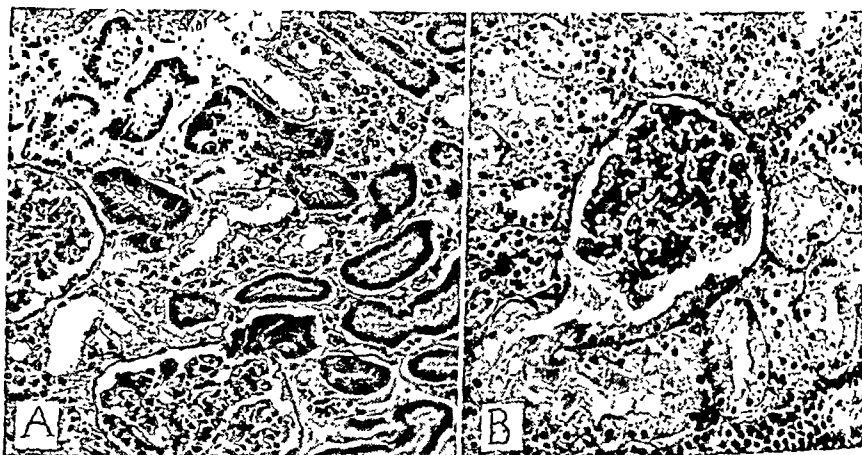


FIG. 1. A, Hypertrophy of epithelium lining convoluted tubules in case of early jaundice. Lumen almost entirely obliterated in some tubules. Glomeruli are free of involvement. Hematoxylin and eosin. B, hypertrophy of tubular epithelium with invagination of cells into capsular space. Jaundice of 2 weeks' duration.



FIG. 2. Hypertrophy of epithelium lining Bowman's capsule. Process almost entirely encircles glomerulus. Marked hypertrophy of cells lining convoluted tubules. Deep jaundice of long duration. Hematoxylin and eosin.

weight from 70 to 295 gm. Four additional rats from the same litter were left unoperated, and eventually sacrificed to provide a small series of normal controls.

Intraperitoneal nembutal anesthetic was used, in doses of 0.05 mg. per gram body weight. Employing sterile technique, the common bile duct of each animal was doubly ligated near the duodenum, through midline celiotomy, the ligature being effected with fine silk thread.

Grossly detectable icterus appeared in nineteen of the rats between the second and fifth postoperative day, heralded by cholemic urine, which stained the peripenile hair and skin, and a short time later by acholic stools. Fourteen of these died from the fifth to the tenth postoperative day, ten with perforation of the distended bile duct, and subsequent bile peritonitis, which was usually fatal within several hours following the onset of shock. Some degree of recanalization of the ducts occurred in the five remaining animals in this primarily jaundiced group. Jaundice cleared entirely in three of these, diminished greatly in one, and cleared entirely in the fifth, to return 20 days later.

In seven rats, recanalization occurred so early that no gross jaundice was detected. Two of these were reoperated, the thickened, somewhat distended ducts doubly ligated and severed, producing intense jaundice for periods of 13 and 23 days respectively. The remaining five were eventually sacrificed. The four control animals were sacrificed at various ages, with overdoses of nembutal.

On the basis of the varied postoperative courses, we may logically divide the series into several interesting categories:

- I. Early intense jaundice, progressing to death in 5-10 days, 14 rats
- II. Early intense jaundice 7 days, diminishing until sacrificed; 28 days total icterus, 1 rat
- III. Early intense jaundice, clearing entirely after 6-19 days, 3 rats
- IV. Early jaundice, clearing, then returning and becoming intense until death; 12 days total icterus, 1 rat
- V. Intense jaundice following reoperation; 13 days and 23 days total icterus, 2 rats
- VI. No jaundice clinically detectable; some thickening and distention of bile ducts, 5 rats
- VII. Control series, 4 normal rats

Of the 21 rats exhibiting clinical jaundice, this was manifest for one week or less in 10 animals, and for more than one week in 11 animals.

A complete autopsy was performed immediately upon the death of each rat. Changes in all viscera were carefully noted and sections made, including at least two sagittal slices from each kidney. Urine specimens were taken from the bladder whenever possible, and examined for bile and cellular elements.

A protocol of each operated animal, including gross and microscopic changes observed, is presented in table 1. Table 2 tabulates the nature and degree of lesions according to duration of jaundice. Some degree of glomerular lesion was produced in 23 rats, a percentage of 88.4.

In general, alterations in Bowman's capsule were most marked in those animals jaundiced for more than one week. In rat 13 (category V) continuously jaundiced for a period of 23 days after 22 days of incomplete bile duct obstruction, a total of 43 per cent of observed glomeruli were involved. There was invagination of hypertrophic epithelium at the tubular pole in 25 per cent, and partial encirclement of Bowman's capsule by the hypertrophic, hyperplastic cells in 18 per cent (fig. 3). In this animal there was gross and microscopic evidence of severe biliary cirrhosis and marked dilatation of pancreatic ducts.

TABLE 1. *Protocol of experimental series*

| RAT NO. | AGE  | WEIGHT AT OPERATION | WEIGHT AT AUTOPSY | ANESTHETIC DOSE | DAY BECAME ICTERIC | TOTAL DAYS ICTERIC | DAY OF DEATH | DIAMETER OF DUCT | DUCT PERFORATED | TUBULAR PRECIPITATE | GLOMERULAR PRECIPITATE | HYPERTROPHY TUBULAR EPITH. | INVASION | HYPERTROPHY CAPSULAR EPITH. | CISTS | OTHER CHANGE                                                                                      | REMARKS                                               |
|---------|------|---------------------|-------------------|-----------------|--------------------|--------------------|--------------|------------------|-----------------|---------------------|------------------------|----------------------------|----------|-----------------------------|-------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------|
|         | days | gms                 |                   | mgm             |                    |                    |              | mm               |                 |                     |                        |                            |          |                             |       |                                                                                                   |                                                       |
| 1       | 35   | 70                  | 56                | 1.5             | 5th                | 3                  | 7th          | 5                | No              | 2+                  | 1+                     | 2+                         | 10%      | 0                           | 2+    | Peritonitis, cystitis                                                                             |                                                       |
| 2       | 38   | 80                  | 50                | 2.5             | 3rd                | 4                  | 6th          | 4                | Yes             | 2+                  | 1+                     | 2+                         | 8%       | 1%                          | 2+    | 50 cc abdominal fluid. No peritonitis                                                             | Lost 18 gm. by 6th day. Recained                      |
| 3       | 39   | 90                  | 95                | 2.5             | 3rd                | 8                  | 10th         | 6                | No              | 2+                  | 2+                     | 2+                         | 10%      | 3%                          | 3+    | Peritonitis, cystitis. 40 cc free bile                                                            | Urinalysis. Bile pos. Clumps WBC. Occ. RBC. No casts  |
| 4       | 39   | 93                  | 75                | 3.0             | 3rd                | 3                  | 5th          | 5                | Yes             | 2+                  | 1+                     | 3+                         | 2%       | 0                           | 0     | Peritonitis, cystitis. 40 cc free bile                                                            |                                                       |
| 5       | 39   | 90                  | 65                | 3.0             | 4th                | 2                  | 5th          | 12               | No              | 2+                  | 1+                     | 3+                         | 0        | 0                           | 1+    | One-plus cirrhosis                                                                                |                                                       |
| 6       | 41   | 110                 | 85                | 3.0             | 1st                | 5                  | 5th          | 12               | No              | 2+                  | 2+                     | 3+                         | 20%      | 10%                         | 3+    | Moderate ileus one-plus cirrhosis                                                                 |                                                       |
| 7       | 58   | 170                 | 135               | 4.5             | 2nd                | 8                  | 9th          | 4                | Yes             | 2+                  | 1+                     | 3+                         | 2%       | 0                           | 3+    | Peritonitis cystitis. 100 cc free bile                                                            |                                                       |
| 8       | 61   | 195                 | 140               | 5.25            | 4th                | 3                  | 6th          | 4                | Yes             | 2+                  | 1+                     | 3+                         | 2%       | 1%                          | 1+    | Peritonitis cystitis. 30 cc free bile                                                             |                                                       |
| 9       | 61   | 190                 | 210               | 5.25            | 3rd                | 19                 | 51st*        | 5                | Yes             | 2+                  | 1+                     | 4+                         | 0        | 0                           | 4+    | Peritoneal and visceral abscesses, 26th day. Tissues anemic. Atrophic spleen. One-plus cirrhosis. | Survived duct perforation. Recannalysed duct 22nd day |

| 10              | 65 | 200 | 205 | 9.0 | 1st | 13 | 13th  | 20  | No  | 3 1 | 1-1  | 3 1- | 15% | 8%  | 3+ | Terminations:<br>clear 3-plus<br>cirrhosis                                                         | with weight lo-<br>gained; nega-<br>tive urinalysis<br>No effect in 24<br>days. Reoper-<br>ated; reexami-<br>ned; reanaly-<br>sed duet sav-<br>ered<br>No effect<br>No effect in 22<br>days. Reoper-<br>ated as in<br>(11)<br>No effect<br>No effect, nega-<br>tive urinalysis<br>No effect<br>Primary jaundice<br>cleared en-<br>tirely with ro-<br>tarn to health<br>6th day |
|-----------------|----|-----|-----|-----|-----|----|-------|-----|-----|-----|------|------|-----|-----|----|----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11              | 65 | 250 | 7.5 |     |     |    |       |     |     |     |      |      |     |     |    | Atrophy spleen;<br>hemorrhagic<br>cystitis; urino-<br>bloody                                       |                                                                                                                                                                                                                                                                                                                                                                                |
| 11 <sup>a</sup> | 89 | 285 | 155 | 12  | 1st | 13 | 13th  | 20  | No  | 3 1 | 1-1  | 3 1- | 15% | 8%  | 3+ |                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                |
| 12              | 67 | 215 | 270 | 7.5 | 0   | 0  | 41st  | 7.5 | No  | 1+  | 1/2+ | 2+   | 3%  | 0   | 1+ | Duet reexami-<br>ned                                                                               |                                                                                                                                                                                                                                                                                                                                                                                |
| 13              | 67 | 235 | 210 | 7.5 |     |    |       |     |     |     |      |      |     |     |    | Anemia, cystitis;<br>fibrosis pun-<br>crens with di-<br>lated ducts 4-                             |                                                                                                                                                                                                                                                                                                                                                                                |
| 13 <sup>a</sup> | 89 | 255 |     | 12  | 1st | 23 | 23rd* | 20  | No  | 2+  | 1-1  | 3+   | 25% | 18% | 3+ | plus cirrhosis<br>Duet thickened,<br>reanalysed                                                    |                                                                                                                                                                                                                                                                                                                                                                                |
| 14              | 67 | 270 | 320 | 7.5 | 0   | 0  | 27th* | 5   | No  | 1+  | 1/2+ | 2+   | 1%  | 0   | 1+ |                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                |
| 15              | 70 | 200 | 310 | 9.0 | 0   | 0  | 30th* | 5   | No  | 2+  | 1+   | 2+   | 3%  | 1%  | 1+ | Duet thickened,<br>reanalysed                                                                      |                                                                                                                                                                                                                                                                                                                                                                                |
| 16              | 70 | 235 | 315 | 8.0 | 0   | 0  | 30th* | 5   | No  | 1+  | 1/2+ | 2+   | 3%  | 1%  | 1+ | Duet thickened,<br>reanalysed, 2-<br>plus cirrhosis                                                |                                                                                                                                                                                                                                                                                                                                                                                |
| 17              | 80 | 230 | 185 | 9.0 | 2nd | 8  | 9th   | 5   | Yes | 2+  | 1/2+ | 3+   | 2%  | 0   | 0  | Acute congestion<br>capillary tufts,<br>peritonitis so-<br>vere. 100 cc<br>free bile               |                                                                                                                                                                                                                                                                                                                                                                                |
| 18              | 80 | 205 | 330 | 12  | 2nd | 5  | 20th* | 5   | No  | 2+  | 1+   | 3+   | 5%  | 1%  | 1+ | Duet thickened,<br>reanalysed.<br>Slight dilata-<br>tion, pancreen-<br>atic ducts, cir-<br>rhosis. |                                                                                                                                                                                                                                                                                                                                                                                |
| 19              | 80 | 225 | 115 | 9.0 | 1st | 8  | 8th   | 0   | Yes | 2+  | 1+   | 3+   | 3%  | 0   | 1+ | Peritonitis, 50 cc<br>free bile                                                                    |                                                                                                                                                                                                                                                                                                                                                                                |

TABLE 1. *Continued*

| RAT NO. | AGE | WEIGHT AT OPERATION | WEIGHT AT AUTOPSY | ANESTHETIC DOSE | DAY BECAME ICTERIC | TOTAL DAYS ICTERIC | DAY OF DEATH | DIAMETER OF DUCT | DUCT PERFORATED | TUBULAR PRECIPITATE | GLOMERULAR PRECIPITATE | HYPERTROPHY TUBULAR EPITH. | INVASION CAPSULAR EPITH. | HYPERTROPHY EPITH. | CASTS | OTHER CHANGE                                                                                                                                                | REMARKS                                                                                                           |
|---------|-----|---------------------|-------------------|-----------------|--------------------|--------------------|--------------|------------------|-----------------|---------------------|------------------------|----------------------------|--------------------------|--------------------|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| 20      | 80  | 295                 | 245               | 18.0            | 3rd                | 5                  | 7th          | 5                | Yes             | 1+                  | ½+                     | 3+                         | 2%                       | 0                  | 2+    | Peritonitis. No free bile. Moderate ileus                                                                                                                   | Icterus intense 7 days. Very slight 21 days                                                                       |
| 21      | 83  | 255                 | 270               | 12              | 2nd                | 7 21 <sup>s</sup>  | 20th         | 7                | No              | 2+                  | 1+                     | 3+                         | 1%                       | 0                  | 1+    | Duct partially recanalysed 2-plus cirrhosis.                                                                                                                |                                                                                                                   |
| 22      | 83  | 265                 | 205               | 12              | 2nd                | 8                  | 9th          | 5                | Yes             | 2+                  | ½+                     | 3+                         | 1%                       | 0                  | 1+    | Peritonitis. 150 cc free bile, cystitis                                                                                                                     |                                                                                                                   |
| 23      | 83  | 250                 | 230               | 12              | 1st                | 7                  | 7th          | 6                | Yes             | 3+                  | ½+                     | 2½+                        | 3%                       | 0                  | 1+    | Peritonitis, 100 cc free bile, cystitis                                                                                                                     |                                                                                                                   |
| 24      | 84  | 270                 | 220               | 12              | 2nd                | 12                 | 25th         | 30               | No              | 3+                  | 2+                     | 3+                         | 10%                      | 8%                 | 3+    | 100 cc free bloody bile. Tubular epithelium bile stained. Atrophyspleen and pancreas. Severe cystitis. 20 per cent of casts bile - stained 4-plus cirrhosis | Icteric 2 - 8th days, then 21-25th days. Urinalysis: granular casts and casts of tubular epith. heavily pigmented |
| 25      | 81  | 265                 | 310               | 12              | 0                  | 0                  | 27th*        | 5                | No              | 1+                  | ½+                     | 1½+                        | 1%                       | 0                  | ½+    | Duct thickened, recanalysed                                                                                                                                 | No effect                                                                                                         |
| 26      | 81  | 210                 | 220               | 12              | 1st                | 6                  | 6th          | 25               | No              | 3+                  | 2+                     | 4+                         | 20%                      | 8%                 | 3+    | Cystitis. One-plus cirrhosis                                                                                                                                |                                                                                                                   |

\* Sacrificed.  
n—Re-operated.

The earliest significant glomerular lesions were seen in 2 rats from category I, jaundiced 5 and 6 days respectively. There was 30 per cent glomerular involvement in one, and 28 per cent in the other, the abnormal cells being essentially confined to the tubular pole.

Complete absence of glomerular capsular lesions occurred in only three rats. These included one animal in category I, jaundiced but two days, and dying after

TABLE 2 Renal lesions with relation to duration of jaundice: Experimental series

|                                                             | ONE WEEK<br>OR LESS | MORE THAN<br>ONE WEEK | NO CLINICAL<br>JAUNDICE |
|-------------------------------------------------------------|---------------------|-----------------------|-------------------------|
| Number of cases                                             | 10                  | 11                    | 5                       |
| Hypertrophy of tubular epithelium                           | 10                  | 11                    | 5                       |
| Invagination hypertrophic epithelium into capsular<br>space |                     |                       |                         |
| 10% glomeruli or more                                       | 3                   | 4                     | 0                       |
| Less than 10% glomeruli                                     | 6                   | 5                     | 5                       |
| None seen                                                   | 1                   | 2                     | 0                       |
| Hypertrophy and hyperplasia of capsular<br>epithelium       |                     |                       |                         |
| 5% glomeruli or more                                        | 2                   | 3                     | 0                       |
| Less than 5% glomeruli                                      | 3                   | 1                     | 2                       |
| None seen                                                   | 5                   | 7                     | 3                       |
| Casts (tubular)                                             | 9                   | 10                    | 5                       |
| Bile stained casts                                          | 0                   | 1                     | 0                       |



FIG. 3 Hypertrophy and hyperplasia of epithelium in Bowman's capsular space, almost completely encircling capsule. Rats jaundiced 23 days. Hematoxylin and eosin.

perforation of the bile duct, and two animals in category III, sacrificed 30 days after an initial intense jaundice had disappeared. The third rat in this category revealed mild involvement of only 6 per cent glomeruli. The lone rat in category II, faintly jaundiced for 21 days after 1 week of intense jaundice, revealed slight alteration in only 1 per cent glomeruli. The paucity of capsular lesions in these animals would seem to lend support to the theory of Thompson, Frazier and

Ravdin<sup>4</sup> that the lesions of cholemic nephrosis are reversible, tending to clear after the influx of bile through the nephrons has ceased, provided the process has not progressed to permanent organic disease.

The five animals comprising category V, in which no grossly detectable jaundice occurred, but bile ducts were partially obstructed, revealed slight involvement of 1-3 per cent glomeruli.

All operated animals revealed moderate to marked hypertrophy of epithelium lining the proximal and distal convoluted tubules. Hyaline casts occupied the distal convoluted and collecting tubules in all animals save two in category I. There was a surprising absence of bile stained casts; however, they were seen in a single rat (category IV) which was intensely jaundiced for 12 days prior to death. Twenty per cent of the casts in this animal's tubules were bile stained. Urine aspirated from the bladder at autopsy revealed the most extensive changes of the entire series. Many casts of tubular epithelium, overlain with brown crystals, were seen. There were many granular casts, and clumps of red and white

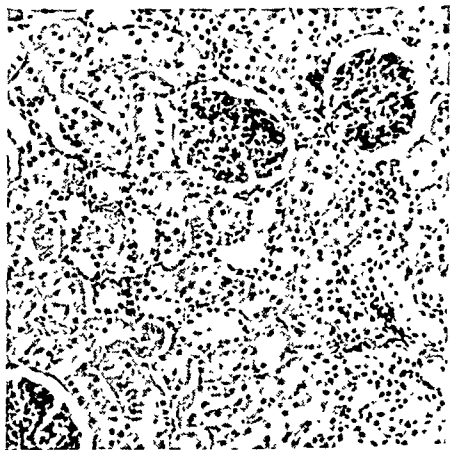


FIG. 4. Kidney from healthy unoperated rat. Hematoxylin and eosin.

blood cells. This animal also revealed an intense hemorrhagic cystitis, the most severe in the series. Eighteen per cent of glomeruli were altered in this animal.

Sections from the four control animals revealed only a moderate hypertrophy of cells lining some distal convoluted tubules, and an occasional loosely packed hyaline cast (fig. 4).

#### SUMMARY AND CONCLUSIONS

On the basis of this study, several conclusions may be stated:

There is evidence that prolonged intense jaundice is capable of producing certain morbid histologic changes within the excretory units of the kidney.

Renal lesions include, in addition to the usually described "swelling" of tubular epithelium and pigmented tubular casts, definite hypertrophy and hyperplasia of epithelium lining the parietal layer of Bowman's capsule. This is a progressive

<sup>4</sup> Thompson, L. L., Frazier, W. D. and Ravdin, I. S.: The renal lesion in obstructive jaundice. *Am. J. Med. Sc.*, 199: 305, 1940.

change, extending from distal to proximal convoluted tubules, invaginating through the tubular pole of the glomerulus, and finally encircling Bowman's capsule. Such lesions were observed in 73.5 per cent of cases in a series of autopsies on jaundiced individuals, and were reproduced in 88.4 per cent of rats subjected to obstruction of the biliary system.

These changes, to a point, are reversible.

The author is indebted to Dr. S. E. Gould, Director of Laboratories, Wayne County General Hospital, for counsel and assistance during the clinical phase of this study, and for making available the autopsy material. Dr. E. T. Bell, Professor of Pathology, University of Minnesota, gave encouragement and helpful criticism by correspondence.

The experimental phase of the study was performed in the experimental laboratories of Alexander Blain Hospital, using animals, materials and equipment furnished by that institution through its Research Fund, sponsored by Dr. Alexander W. Blain.



## SEXTUPLICITAS RENUM: A CASE OF SIX FUNCTIONING KIDNEYS AND URETERS IN AN ADULT FEMALE

R. CAMPBELL BEGG

Radiographic evidence indicates the presence of six complete and functioning kidneys in the case to be described. Some of the corresponding kidneys may have been fused with each other but this does not detract from their individuality for, as Gruber (1906) rightly points out, there is genetically no difference between supernumerary kidneys whether their blastema has fused or not. The patient, Mrs. X, a 42 year old married woman, enjoyed such excellent health both before and after the incident of central abdominal colic which led to the x-rays being taken, that she saw no reason for further investigation to satisfy the curiosity of science. However, the pictures taken by Drs. Charlton, Loots and Osler, to whom I am indebted for them, are of excellent quality and clearly indicate that the six kidney-ureter units consist of two sets of three each (figs. 1 and 2). There is a medial group consisting of a single right and a double left unit, and a lateral group which also shows a single kidney on the right and two on the left. The two sets differ from each other in position and character. The medial one taken alone would not excite interest because it reproduces a very common clinical finding, namely a double kidney and two ureters on one side. The two ureters run close together and reach the bladder at approximately the same place. In the lateral group, on the other hand, all three ureters pass out widely and maintain a course far lateral to the normal one. They originate from no well-defined kidneys but by a series of tube-like calyces which pass mediolaterally, in contrast to the usual arrangement as seen in the medial group. At their lower ends, these lateral ureters turn sharply towards the middle line, cross the medial ureters, and seem to be coursing towards the region of the bladder neck. The two left lateral ureters run side by side and appear to cross one another at least once.

Another point of difference which is of importance and will be referred to later, is that the medial set is doing most of the work. In its three components the concentration of the uroselectan is greater and more prolonged and the ureters are clearly defined even in the 40 minute film. The shadows of the lateral ureters, on the contrary, are seen to be paler from the outset and cease to be visible after the ten minute film.

### ORIGIN OF THE ANOMALY

It is interesting to speculate on the embryological disturbance that could have produced such an unusual urinary tract and still left the general health unimpaired. One might marshal the hypotheses as follows:

- 1) There were only two mesonephric ducts, but two ureteric buds arose from the right one and four from the left.
- 2) The lateral ureters represent a mesonephric system which has continued to function in the adult. The mesonephric duct of the left side is duplicated.

3) There were four mesonephric ducts in the embryo, two on each side. The ones on the right side gave rise to one ureteric bud each, those on the left to two each.

4) The extra kidneys and ureters represent a teratomatous formation, and there is a "duplicitas infraumbilicalis" present with no manifestations outside the urinary tract.

Some detailed consideration may now be given to each of these theories.

1) *The theory of multiple ureteric buds.* This is the commonly accepted explanation for the presence of multiple ureters and is a reasonable supposition to account for the customary three- or four-kidney subject. In these cases the ureters run more or less together and open somewhere along a line from the supero-



FIG. 1. Ureteric urogram showing six ureters. Film taken 10 minutes after injection of 20 cc of uroselectan. Lateral three ureters show much less concentration of dye than medial ones.

lateral corner of the trigone to the verumontanum in the male, or the vestibule of the vagina in the female. In a previous paper (1927) I gave some consideration to this development vagary. In the few cases of triple kidney that have been described, the three ureters ran together and the condition was, in theory, capable of explanation, by pre-supposing three buds on one side. Eisendrath and Rolnick (1943) devote a short paragraph in their book to the subject of triple ureters and emphasize the rarity of the condition, quoting the cases of Lau and Henline (1931) and of Chwalla of Vienna (1935). In both these instances, there were three ureters on the right. They ran side by side but one of them ended blindly after a short upward course. Gruber refers to a communication of Preissler, who found, in an ox, three kidneys inside the fatty capsule of the left side,

One must be careful in regard to terminology as the expression "triple kidney" may, as in Hanley's case (1942), refer to a horseshoe kidney with a *total* of three ureters. I have not had access to Chwalla's article, but Lau and Henline, who wrote very shortly after the introduction of excretory urography, give an interesting historical review on the subject of multiple ureters. They quote Cunningham of Boston as saying that he was almost sure that he had encountered a case with six ureters. This vague reference seems to constitute the only previous mention of such a condition. Subsequently, Woodruff (1941) reported a case in which a routine pyelography in a prostatic disclosed three definite kidney-ureter units on the right side and one on the left. The case is illustrated and shows a true triple kidney with good function in all its components, the ureters running together, and the calyces all draining latero-medially into the pelves in the normal manner.

It seems, however, that the case of Mrs. X is unique in that there are two *sets* of kidneys each different to the other in location and behavior, while the individual components of each set are similar to each other in both these respects.

2) *Theory of a functioning mesonephric system.* At the first blush, the finding of a functioning mesonephric system in an adult human being would be about equivalent to meeting a grazing Brontosaur in Regent's Park! Incidentally "extinct" species have occasionally turned up unexpectedly in living form. For example among the birds, *Notornis* in New Zealand, and among the fishes *Latimeria Chaumnae* in South Africa. Thus far-fetched as the mesonephric theory may appear to be, there are certain features in the case of Mrs. X which may be considered to support it. These may be summarised shortly as follows:

a) As previously mentioned, the lateral ureters lie far out and at the caudal extremity turn sharply medially and cross the medial ureters. It is impossible to tell from the x-rays whether the lateral ureters are anterior at the point of crossing as they should be if they represent mesonephric ducts. These ureters are supplied by a series of tube-like calyces somewhat segmental in character which originate in a rather indefinite medial mass and run laterally to join the ureters. In all these respects they recall the arrangements existing in the mesonephros and its ducts. The comparison is illustrated in figures 2 and 3.

b) In the films of Mrs. X, the order of the structures, latero-medially are: lateral ureters, indefinite mass from which the calyces emerge, kidney and medial ureters. This corresponds to the order in the fetus which is: Mesonephric (wolffian) duct, mesonephros (wolffian body), kidney and ureter.

c) The lateral secreting units, it has been shown, play a very minor role in comparison with the medial ones. This is what one would expect of mesonephric units functioning faintly long after they should, in the ordinary course of events, have disappeared entirely or, at most, be represented by a few inactive fragments in the mesosalpinx. They are hardly more than shadow or ghost kidneys. This is a very different state of affairs from that which is found in the aplastic unit of double kidney which, unless diseased, concentrates urine as well, and for as long a time, as the major component of the same organ.

Turning from these anatomical comparisons to evolutionary evidence, one is

able to find in the animal world instances in which mesonephric and metanephric systems function simultaneously. According to Pellegrin (1914) there are some



Fig. 2. Semi-diagrammatic representation of urinary tract of Mrs. X, derived from study of whole series of films for comparison with figure 3. On left side, lateral ureters are shown passing behind medial ones, and on right lateral ureter passes in front. Actually it was impossible to be sure whether crossing was in front or behind on either side

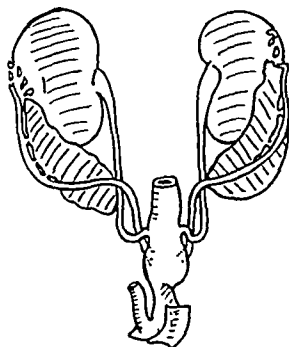


Fig. 3. Drawing to show genito-urinary tract in a 23 mm. fetus. Mesonephros and its duct are seen to be lateral to kidney and ureter and duct crosses anterior to ureter. (After Hunter, R. H., Contrib. to Embry No. 129, 1930)

lizards (*Iacerta*) in which this occurs for more than the first year of life. Gegenbaur (1901) writing 13 years earlier had stated: "The abandonment by the mesonephros of its excretory function and the accompanying retrogression in its

structure does not take place in reptiles till a long time after the animal has left the egg. The lacerta in which the conditions have been best studied have a mesonephros which operates until after the first winter sleep" (author's translation). Thus were it possible to get pyelograms of a leguan or a monitor early in life, one would expect to get pictures similar to those of Mrs. X except that normally neither of the two ureters on the left side would be double!

Kermauner of Vienna (1909), writing in the first edition of Schwalbe's book on malformations of the female genital tract, mentions a case of Skene's (1896) in which this author passed a sound up a duct opening close to the external urethral meatus and coursing up alongside the uterus. This canal was afterwards cauterized and partially removed because of the annoyance to the patient caused by the fluid which was excreted. "Kein Harn!" annotated Kermauner when recording this observation, but is it so certain after all that it was not urine? The situation of the canal makes it probable that it was a Gaertner's duct, that is, a persistent mesonephric channel. It might, of course, have been an aberrant ureter which, when present, regularly opens just below or beside the external urethral meatus in the female. Skene, however, was certain that its course lay along the uterus, thus following the normal track of a persistent mesonephric or wolffian duct. Is it possible that in this case the conduit was carrying the watery urine of a functioning mesonephros?

3) *Duplication of the mesonephric duct.* A priori, there seems to be no reason why the mesonephric duct should not be duplicated as readily as the metanephric ureter. Neale and Rand (1936) after referring to the confusion between mesonephros and metanephros at the phylogenetic level at which the one is being replaced by the other, conclude: "The fact that in some mammals and in man a number of ureters may develop suggests the possibility that ureters were primitively multiple but that they have become reduced in number in mammals." I have not searched zoological literature, and do not know whether double ureters have been found in such animals as frogs and toads which use a mesonephric system of excretion, but I have little doubt that this anomaly must occasionally occur.

On this point there is some evidence to be derived from the human subject. When three testicles and their vasa deferentia are found in an adult male, there is a strong presumption that there were three mesonephric ducts in the embryo from which he was derived, as the vas in the man represents a later stage of the primitive urinary channel of the fetus. The condition of multiple testes is rare, and in most of the reports under this heading there is merely a fission of one testicle, one vas serving both parts. However, Edington and Blacklock (1928) in a comprehensive review picked out four cases in which a third vas and corresponding testis were present. The reporting authors were Lane (1894), Mariotti (1907), Hass (1922) and Holder (1925). I have looked up a number of articles published since Edington and Blacklock's paper appeared, but have not been convinced by the descriptions given that an extra vas was actually present. Lane's case was of interest. He found one normal testis on the left side and two on the right each with its tunica vaginalis and its vas deferens. The upper and smaller testis on

the right side was removed at the request of the patient, an adolescent who did not relish this superabundance of nature's gifts. The only discussion when the case was presented to the Clinical Society of London was by a surgeon present, who took Lane to task for wantonly interfering with an organ that had been, for some good purpose, bestowed by Providence on its owner! From the above instances of multiple vasa and testes in the adult, it seems that there may be three mesonephric ducts in the fetus; and if three, why not four, a condition which might lead to the phenomena under review, as found in Mrs. X? We should have to assume that one ureteric bud arose from each of the right mesonephric ducts and two from each of the left ones.

4) *Theory of developmental duplicity.* The hypothesis of developmental duplicity is based on the possibility of another fetus being superimposed, a kind of teratoma, where the lateral set of ureters would pertain, as it were, to a different individual, a very restricted case of Siamese twins. I am grateful to Professor H. A. Harris of the Cambridge School of Anatomy for sending me an article by Gruber on this subject. The chapter by this author appears in a later edition of Schwalbe's *Missbildungen* than the one to which I have access. Gruber refers to a report by Altmann (1926). The latter dissected a three day old ibex of undetermined sex. There were two ureters and kidneys in the normal position. In addition, there were two rudimentary kidneys, and the corresponding ureters opened respectively into the urethra and into a canal lying parallel to it. The animal had a split pelvis, a supernumerary extremity, persisting cloacal arrangements, and, apparently, a double urethra. There was a small tube, blind at both ends, which Altmann interpreted as a fifth ureter. The condition present in this young animal is that denoted by Schwalbe as "*Duplicitas asymmetros ventralis infraumbilicalis.*" It would be difficult to accept the duplicitas hypothesis in the case of Mrs. X, a woman to all outward appearance perfectly formed, and normal as regards physiology and reproduction.

#### CONCLUSION

None of the theories brought forward are particularly convincing. That of two mesonephric ducts with six ureteric buds fails to account for the three poorly functioning and laterally situated ureters. That the latter are in fact mesonephric is supported by their position and the other arguments brought forward. One must assume a double wolffian duct on the left side, but this has been shown to be an occasional possibility. The difficulties in accepting this theory are:

The paramesonephric (müllerian) ducts are intimately connected with the mesonephric ones crossing them lateromedially and being wrapped up with them in the genital cord. Now, in the case of Mrs. X, the genital system was normal enough to permit her to mother two healthy boys. With the paramesonephric system thus developing along the usual lines, it is difficult, but perhaps not impossible, to conceive that the mesonephros and its duct should remain at the early foetal stage.

The ovary must lie adjacent to the mesonephros, so that if the ovaries in the case under review were in the pelvis, the body high up near the kidney could not

be a persistent mesonephros. What is not known is whether the ovaries actually were in the pelvis or whether children could be conceived if they were not.

The customary opening of a persistent wolffian duct (Gaertner's duct) lies distal to the external sphincter of the urethra implying incontinence of urine which the patient did not have. Possibly on occasion it opens at a higher level within the sphincter, but there is no evidence that this is so.

It is stated that the mesonephros never functions even for a moment in the human fetus. This statement, often made, lacks proof, and even if true in a general way would doubtless in the hurly-burly of development be subject to exceptions.

The third theory that there were four mesonephric ducts and six ureteric buds does not elucidate the different nature of the lateral from the medial ureters, and presupposes an anomaly of an unprecedented kind. The fourth or "Duplicitas" theory is inherently improbable.

In fine, all one can say is that that the anomaly occurred, that it is unique, and that the attempt to explain it is as hopeless a task as that of the philologist trying to piece out a dead language from limited material and finding instances where a word occurs only once in the manuscripts, and then with no adequate context to indicate its meaning.

#### SUMMARY

A case is described in which six functioning kidneys and ureters were found by radiography in an adult female.

The ureters appeared in two sets, each set showing different characteristics both as regards position and function.

Four hypotheses are discussed in an endeavor to explain how the anomaly arose, but none of these is entirely satisfactory.

The hypotheses are:

Two mesonephric ducts but six ureteric buds, two on one side and four on the other.

Persistent functioning mesonephric units with a double duct on the left side, together with one single and one double metanephric unit, making six in all.

Four mesonephric ducts giving rise to six ureteric buds.

Duplicity (teratoma) of the hinder end of the body.

*152 Lister Bldg., Johannesburg, South Africa*

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It is stated that the mesonephros never functions even for a moment in the human fetus. This statement, often made, lacks proof, and even if true in a general way would doubtless in the hurly-burly of development be subject to exceptions.

The third theory that there were four mesonephric ducts and six ureteric buds does not elucidate the different nature of the lateral from the medial ureters, and presupposes an anomaly of an unprecedented kind. The fourth or "Duplicitas" theory is inherently improbable.

In fine, all one can say is that the anomaly occurred, that it is unique, and that the attempt to explain it is as hopeless a task as that of the philologist trying to piece out a dead language from limited material and finding instances where a word occurs only once in the manuscripts, and then with no adequate context to indicate its meaning.

#### SUMMARY

A case is described in which six functioning kidneys and ureters were found by radiography in an adult female.

The ureters appeared in two sets, each set showing different characteristics both as regards position and function.

Four hypotheses are discussed in an endeavor to explain how the anomaly arose, but none of these is entirely satisfactory.

The hypotheses are:

Two mesonephric ducts but six ureteric buds, two on one side and four on the other.

Persistent functioning mesonephric units with a double duct on the left side, together with one single and one double metanephric unit, making six in all.

Four mesonephric ducts giving rise to six ureteric buds.

Duplicity (teratoma) of the hinder end of the body.

152 Lister Bldg., Johannesburg, South Africa

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## WILMS'S TUMOR IN CHILDREN

ROBERT A. GARRETT AND H. O. MERTZ

*From the Department of Genito-Urinary Surgery, Indiana University Medical Center, Indianapolis, Ind.*

The management of renal embryomas in children (Wilms's tumor) is a dynamic subject. Despite the fact that approximately the same therapeutic methods were available a decade and a half ago, the expectant cure rate has improved from approximately 10 per cent to currently better than 33 per cent. It has been repeatedly asserted that renal embryomas make up 20 per cent of all neoplasms of childhood, being surpassed only by tumors of the eye. We believe that further observations on this problem are warranted.

The material for this paper is derived from 78,961 admissions to the James Whitcomb Riley Hospital for Children over the period 1925 to 1949 inclusively. Twenty three consecutive cases of Wilms's tumor have been observed over this 25 year period, of which eight have survived and fifteen are dead. Nineteen of these 23 cases were managed exclusively by the staff, whereas the remaining were referred to the hospital after nephrectomy elsewhere. Usually the problem was that of terminal care in the latter four. There is little predilection for side or sex, although our series does not bear this out. Eight were females and 16 were males. The left side was involved in 14 cases, the right in 10. Sixteen of our cases were three years of age or less, while 8 were over 3 years. This is in keeping with Campbell.<sup>1</sup>

The classic description of renal embryomas by Wilms<sup>2</sup> in 1899 has linked his name to these neoplasms, although Gairdner<sup>3</sup> first noted their existence in 1828, and Birch-Hirschfeld,<sup>4</sup> in 1894 described and emphasized the multiple types of tissue found therein.

Histogenesis of these tumors was formerly attributed to aberrant rests of sclerotome and myotome, or to aberrant growth of the wolffian body. The concept of Muus<sup>5</sup> in part shared by Wilms and further supported by Dean<sup>6</sup> relates the tumor to the renal blastema, thus satisfactorily explaining the multiplicity of histologic patterns encountered. The occurrence of approximately three microscopic classes of tumors based on the date of origin in embryonic life has been described by Geschickter and Widenhorn.<sup>7</sup> The first class predominates in elements foreign to the kidney (muscle, bone, cartilage). The majority of Wilms's tumors fall into the second class, predominating in abortive tubules surrounded by small spindle cells arranged in whorls. The third class is rather unusual and is found to contain more adult elements (embryonic glomeruli and tubules).

Accepted for publication April 25, 1952.

<sup>1</sup> Campbell, M. F.: *Clinical Pediatric Urology*. Philadelphia: W. B. Saunders Co., 1951.

<sup>2</sup> Wilms, M.: *Die Mischgeschwülste der Nieren*. Leipzig: Arthur Georgi, 1899.

<sup>3</sup> Gairdner, E.: *Edinburgh Med. and Surg. J.*, 29: 312, 1828.

<sup>4</sup> Birch-Hirschfeld, F.: *Centralblatt f. d. Krankh. d. Harn und Sexual-Organie*, 5: 88, 1894.

<sup>5</sup> Muus, N. R.: *Virchows Arch. f. path. Anat.*, 155: 401, 1899.

<sup>6</sup> Dean, A. L.: *N. Y. State J. Med.*, 45: 1213, 1945.

<sup>7</sup> Geschickter, C. F. and Widenhorn, H.: *Am. J. of Cancer*, 22: 620, 1934.

All of our patients had a palpable mass in the abdomen on hospital admission. The majority of parents reported accidental discovery of the mass, commonly while bathing the child. In contradistinction to the findings in hypernephroma, hematuria is not a common initial complaint. But few of our patients manifested hematuria.<sup>6</sup> Some degree of discomfort was registered by seven, and was usually vague and unlocalized. Tumor growth is usually rapid, changes in size being noted from one week to the next in untreated cases. Hemorrhage into the tumor accounts for sudden overnight growth.

On examination the abdomen is commonly found enlarged, distended asymmetrically by the loin mass. The superficial abdominal veins may be unusually discernible. Palpation of the mass by ballottement should be done sparingly and gently. Some degree of mobility can usually be elicited inasmuch as tendency for local tumor spread beyond the capsule does not occur until late. This should be borne in mind before declaring a tumor inoperable, thus avoiding the error of allowing an operable tumor to go unexplored. Fever is not a rare finding in the absence of demonstrable infection. Hyperpyrexia was the dominant finding in one of our cases, terminating rapidly in death before therapy of any kind could be instituted.

Diagnosis is not difficult. A loin mass in a child should arouse suspicion. Employment of the excretory pyelogram often is diagnostic. Moreover it will determine the integrity of the opposite kidney. Distortion of the calyceine pattern by pressure, with medial, anterior or inferior displacement is the rule. Superior displacement may occur but is uncommon. Lateral displacement is rare. Retrograde pyelography may be and often is utilized when any doubt exists. Other abdominal lesions must be excluded in the differential diagnosis. Pyelography usually excludes hydronephrosis, the most frequent urinary tract tumor in children. Neuroblastomas often have a characteristic peppering of calcific deposits, and are less apt to distort the calyceine pattern. Pyelographic distortion by adrenal neoplasms may simulate renal embryoma, although usually pelvic displacement is downward and outward with little calyceine compression. The differential diagnosis of a renal cyst may be difficult and answered only at exploration. Radiotherapy may be of some diagnostic value in such a case. Of course polycystic disease is bilateral and characteristic pyelographically. The problem of splenomegaly is solved at pyelography, as a rule.

Treatment is controversial. Several methods of management are available, utilizing surgery, radiotherapy or a combination of both. There is little disagreement that nephrectomy must be employed to realize a creditable cure rate, although several cures have been reported with radiation alone.<sup>6, 8, 9, 10, 11, 12, 13, 14</sup> The greatest disputation centers about the proper use of radiotherapy. In a

<sup>6</sup> Nesbit, R. M. and Adams, F. M.: *J. Pediat.*, **29**: 295, 1946.

<sup>7</sup> McNeill, W. H. and Chilko, A. J.: *J. Urol.*, **39**: 287, 1938.

<sup>10</sup> Sauer, H. R.: *N. Y. State J. Med.*, **48**: 497, 1948.

<sup>11</sup> Kerr, H. D.: *J.A.M.A.*, **112**: 408, 1939.

<sup>12</sup> Dickey, L. B. and Chandler, L. R.: *Pediatrics*, **4**: 197, 1949.

<sup>13</sup> Bixler, L. C., Stenstrom, K. W. and Creevy, C. D.: *Radiology*, **42**: 329, 1944.

<sup>14</sup> Pohle, F. A. and Ritchie, G.: *Radiology*, **24**: 193, 1935.

recent exhaustive review of the literature, Harvey<sup>15</sup> was unable to establish good statistical evidence to support any one form of therapy. However, Ladd<sup>16</sup> and later Gross,<sup>17</sup> reporting in 1950, advocating immediate surgery, recorded 2 year cure rates of 30 per cent and 47.3 per cent respectively. The latter attributes this improvement at the Boston Children's Hospital to the additional use of postoperative x-ray. On the other hand, Priestley,<sup>18</sup> Rusche,<sup>19</sup> Kretschmer,<sup>20</sup> Prather,<sup>21</sup> and many others favor the use of preoperative x-ray as well as postoperative radiation. Perhaps a more rational approach to the problem is to consider each case individually, using preoperative therapy in those cases in which the operator feels nephrectomy too formidable, reserving immediate surgery for smaller neoplasms. This view is held by Nesbit,<sup>8</sup> and Sauer.<sup>10</sup> Indeed, it is our belief that preoperative x-ray should be administered only until the neoplasm is reduced to operable dimensions, leaving intense radiation to the postoperative phase. We believe that postoperative radiotherapy is desirable and use it routinely.

Of the 19 patients undergoing therapy primarily at the Indiana University Medical Center, nine underwent nephrectomy. Of these, eight are living and well 18 months or more. Of the remaining ten, one died in hyperpyrexia prior to institution of therapy, two were considered inoperable at surgical exploration, and seven were denied exploration as inoperable. By more recent standards, many of those considered inoperable might now be nephrectomized. Of the 9 patients undergoing extirpative surgery, four had transabdominal and five had lumbar nephrectomies. All of those considered inoperable were submitted to x-ray therapy to the limit of their tolerance. All are dead. The operative mortality was zero. Table 1 has been constructed to illustrate the methods of management employed in the 19 cases analyzed. Table 2 includes those cases having nephrectomy elsewhere.

The amount and technique of x-ray therapy over the 25 year period has varied. Currently the factors in technique are as follows: 20 ma current, 200 KV through 50 centimeters of air with  $\frac{1}{2}$  mm. Cu and 1 mm. Al (0.9 mm. Cu HVL) filtration. Ordinarily the daily dose administered to one of three abdominal ports in rotation will fall between 100-200 r. Ultimately up to 2,000 r to each field is delivered, achieving a dose of from 3000 to 3500 r at the center of the tumor. The amount delivered prior to surgery is dependent upon the response of the tumor to roentgen therapy. If response is rapid, rendering the kidney easily operable in a short period, the majority of the x-ray therapy will fall in the postoperative phase. Individual tolerance will influence the amount of dosage delivered. It is also to be emphasized that the amount of radiotherapy delivered is dependent upon the time interval consumed in administering it.

Heavy local radiation may cause skeletal defects due to epiphyseal arrest.

<sup>15</sup> Harvey, R. M.: *Radiology*, **54**: 689, 1950.

<sup>16</sup> Ladd, W. E. and White, R. R.: *J.A.M.A.*, **117**: 1858, 1941.

<sup>17</sup> Gross, R. E. and Newhauser, E. B. D.: *Pediatrics*, **6**: 843, 1950.

<sup>18</sup> Priestley, J. T. and Schulte, T. L.: *J. Urol.*, **47**: 7, 1942.

<sup>19</sup> Rusche, C.: *J. Urol.* **65**: 950, 1951.

<sup>20</sup> Kretschmer, H. L.: *Arch. Surg.*, **41**: 370, 1940.

<sup>21</sup> Prather, G. C. and Friedman, H. F.: *N. Eng. J. Med.*, **215**: 655, 1936.

This is demonstrated in two of our series. In both, maturation of the ilium on the radiated side failed to occur (fig. 1). Functionally there has been no handicap noted in either. This is a small price to pay in view of the apparent beneficial tumor effect.

Metastasis of renal embryomas proceeds by way of the blood stream in the main, although lymphogeneous dissemination may occur. Lung and liver are involved first, with ultimate spread being widespread. Bone metastasis is uncommon and serves as a point of differentiation between neuroblastoma and Wilms's tumor. The former is notorious in its bone metastasis. Local spread through the thick tumor capsule proceeds slowly and takes place late in the

TABLE 1. *Therapeutic statistics. Cases exclusively I. U. Medical Center*

|                                                         | OUTCOME   |            |
|---------------------------------------------------------|-----------|------------|
|                                                         | Alive     | Dead       |
| No therapy                                              | 0         | 1          |
| Nephrectomy and postoperative x-ray                     | 1         | 0          |
| Preoperative x-ray and nephrectomy                      | 2         | 0          |
| Preoperative x-ray, nephrectomy and postoperative x-ray | 5         | 1          |
| Radiation only                                          | 0         | 9          |
| Total                                                   | 8 (42.1%) | 11 (57.9%) |

TABLE 2. *Therapeutic statistics. All cases*

|                                                         | OUTCOME   |            |
|---------------------------------------------------------|-----------|------------|
|                                                         | Alive     | Dead       |
| No therapy                                              | 0         | 1          |
| Nephrectomy and postoperative x-ray                     | 1         | 4          |
| Preoperative x-ray and nephrectomy                      | 2         | 0          |
| Preoperative x-ray, nephrectomy and postoperative x-ray | 5         | 1          |
| Radiation only                                          | 0         | 9          |
| Total                                                   | 8 (34.8%) | 15 (65.2%) |

course of the disease. It is possible that radiotherapy may obliterate this type of growth, thus rendering it more readily operable. An unusual metastasis to the urinary bladder was observed in one of our series, previously reported.<sup>22</sup> It is of extreme importance to consider a significant number of metastatic cases salvageable. In the series here considered two children have survived 4½ years and 18 months free of disease after x-ray obliteration of pulmonary metastases. Their case reports appear below. Although pulmonary fibrosis may result from heavy thoracic radiation, little is lost in attempting salvage of these children. Neither of the children demonstrate damaged pulmonary fields today. Success in radia-

<sup>22</sup> Mertz, H. O., Howell, R. D. and Hendricks, J. W.: J. Urol., 46: 1103, 1941.

TABLE 3. *Wilms' tumors, 1925-1949 (25 years)*

| AGE    | SYMPTOMS |      |           |      | TREATMENT              |                               |                        | LENGTH SURVIVAL         | COMMENTS                                                                |
|--------|----------|------|-----------|------|------------------------|-------------------------------|------------------------|-------------------------|-------------------------------------------------------------------------|
|        | Side     | Mass | Hematuria | Pain | Initial x-ray          | Surgery                       | Postop. x-ray          |                         |                                                                         |
| 2 yr.  | L        | +    | +         | +    | Yes. Amt. not recorded | None                          | —                      | Deceased 2½ mos.        | Considered inoperable                                                   |
| 2 yr.  | L        | +    | +         | —    | Yes. Amt. not recorded | Laparotomy tumor not operable | None                   | Deceased 11½ mos.       |                                                                         |
| 1½ yr. | L        | +    | —         | —    | None                   | Transperitoneal               | Yes. Amt. not recorded | Living and well 11 yrs. | Lost to follow-up after 11 year survival. Probable cure                 |
| 3½ yr. | R        | +    | —         | —    | 1800 r                 | None                          | —                      | Deceased 4 mos.         | Lung metastasis                                                         |
| 1½ yr. | R        | +    | +         | —    | Yes. Amt. not recorded | None                          | None                   | Deceased 4 mos.         | Tumor thought inoperable<br>Autopsy revealed no extension or metastasis |
| 3 yr.  | L        | +    | —         | +    | 3,000 r                | None                          | —                      | Deceased 1 mo.          | Metastasis to lung                                                      |
| 11 yr. | L        | +    | +         | +    | 14,600 r               | None                          | —                      | Deceased 14½ mos.       | Had metastasis to urinary bladder; biopsy diagnosis                     |
| 11 yr. | R        | +    | —         | +    | 2,000 r                | None                          | —                      | Deceased 2½ mos.        | Little or no response to x-ray; no biopsy                               |
| 6 mo.  | R        | +    | —         | +    | None                   | None                          | —                      | Deceased 4 days         | Extreme hyperpyrexia contraindicated therapy; no biopsy                 |

|   |        |   |   |   |                                   |                                      |                             |                             |                                                       |
|---|--------|---|---|---|-----------------------------------|--------------------------------------|-----------------------------|-----------------------------|-------------------------------------------------------|
| P | 5 yr   | L | + |   | 2,800 r flank                     | Transperitoneal                      | None                        | Living and well<br>8½ yrs.  | Lost to follow-up after 8½ yrs. Probable cure         |
| M | 5 mo   | R | + | - | 5,400 r                           | Posterolateral                       | 3,000 r                     | Living and well             | Response to x-ray long delayed. Probable cure         |
| F | 5 yr   | L | + | - | 1,200 r abdomen,<br>3,400 r chest | None                                 |                             | Deceased 8 mos.             | Metastasis after initial x-ray course (lung)          |
| M | 2½ yr  | L | + | + | 21,630 r                          | Posterolateral                       | 2,000 r                     | Living and well<br>11½ yrs. | Preoperative x-ray for 2 years. Probable cure         |
| M | 1 yr   | L | + | - | 8,200 r                           | Transperitoneal                      | None                        | Living and well 5 yrs.      | Epiphyseal arrest of left ilium. Probable cure        |
| M | 1 yr   | L | + | + | 3,200 r                           | Plank exploratory tumor not operable | No                          |                             | Lost to follow-up. Almost certainly deceased          |
| M | 6 yr   | R | + | - | 3,700 r                           | Posterolateral                       | 3,000 r flank, 3,000 r lung | Deceased 10½ mos.           | Inoperable at laparotomy prior to x-ray therapy       |
| F | 3½ yr  | R | + | - | 3,000 r                           | Posterolateral                       | 1,200 r lung                | Living and well<br>1½ yrs.  | Metastasis to lung; responded to x-ray. Probable cure |
| F | 3 yr.  | L | + | + | 3,300 r                           | Posterolateral                       | 1,000 r flank, 1,000 r lung | Living and well<br>3½ yrs.  | ?? Lung metastasis; radiated                          |
| F | 2½ yr. | L | + | - | 2,400 r                           | Transperitoneal                      | 2,400 r flank, 1,300 r lung | Living and well<br>18 mos.  | Single chest metastasis. Responded to x-ray           |



TABLE 3.—*Concluded*  
*Wilms's tumors treated primarily elsewhere; admitted for x-ray therapy*

| AGE    | SYMPTOMS |      |           |      | TREATMENT     |                               |                              | LENGTH SURVIVAL  | COMMENTS                                                                  |
|--------|----------|------|-----------|------|---------------|-------------------------------|------------------------------|------------------|---------------------------------------------------------------------------|
|        | Side     | Mass | Hematuria | Pain | Initial x-ray | Surgery                       | Postop. x-ray                |                  |                                                                           |
| 8½ yr. | R        | +    | +         | —    | None          | Transperitoneal               | 3,000 r flank, 3,100 r lung  | Deceased 5 mos.  | Wrong diagnosis                                                           |
| 2 yr.  | L        | +    | —         | +    | None          | Laparotomy; tumor not removed | 2,800 r                      | Deceased 2 mos.  |                                                                           |
| 3 yr.  | L        | +    | +         | —    | None          | Transperitoneal               | 3,600 r lung, 3,200 flank    | Deceased 5 mos.  | Admitted with local recurrence; subsequent lung metastasis                |
| 2½ yr  | R        | +    | ?         | ?    | None          | Transperitoneal               | 7,100 r flank, 5,800 r lungs | Deceased 16 mos. | Came to L. U. M. C. with massive abdominal recurrence and lung metastasis |

tion of pulmonary metastases has previously been reported by Kerr,<sup>11</sup> Bixler, Stenstrom and Creevy<sup>13</sup> and Silver.<sup>23</sup>

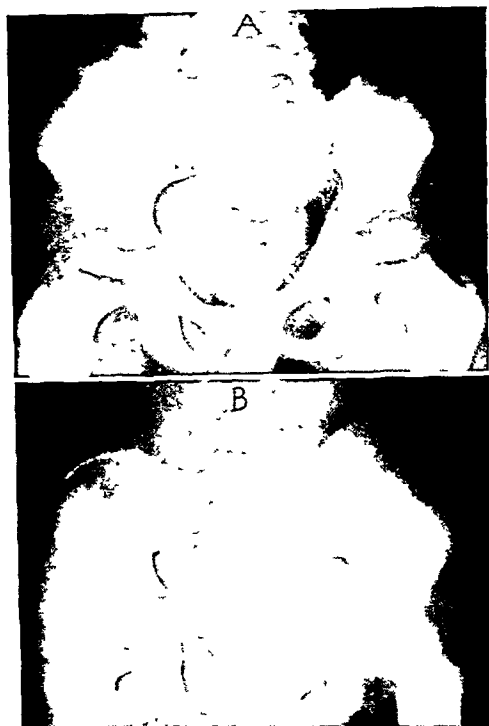


FIG. 1. A, epiphyseal arrest of left ilium 8200 r x-ray administered B, epiphyseal arrest of right ilium 8400 r x-ray delivered



FIG. 2 A, hilar metastasis on right side noted March 15, 1947 B, normal chest x-ray, July 27, 1951

#### CASE REPORTS

*Case 1* E. H. K (104329), a 3½ year old white girl, was admitted to the hospital on November 11, 1946. A mass had been found under her right rib margin 3 days prior to admission. The child had been in the best of health and

<sup>23</sup>Silver H K J Pediatr. 31: 643, 1947

spirits. Unusually prominent abdominal veins were noted at the time of tumor discovery. On examination a mass occupying the entire right flank and abdomen, extending downward into and filling the iliac fossa was found to be slightly mobile. The blood pressure was 95/70. Blood count and urinalysis failed to disclose abnormalities other than mild anemia. Chest and long bone x-rays were normal. An excretory urogram, later confirmed by retrograde pyelography, pointed out a large soft tissue mass in the right flank with pelvic distortion typical of Wilms's tumor. X-ray therapy was begun immediately, delivering 3000 r to three abdominal ports over a period of 17 days. Response was striking after the third day of therapy. A lumbar nephrectomy was done on the eighteenth day of therapy. Radiation was not resumed after surgery. The child was discharged in good condition on January 3, 1947. A follow-up chest x-ray on March 15, 1947 revealed a definite area of metastatic deposit in the right hilar region with other questionable deposits in both lung fields (fig. 2, A). A second course of x-ray was directed toward both lung fields. A total of 4200 r was given. The hilar mass

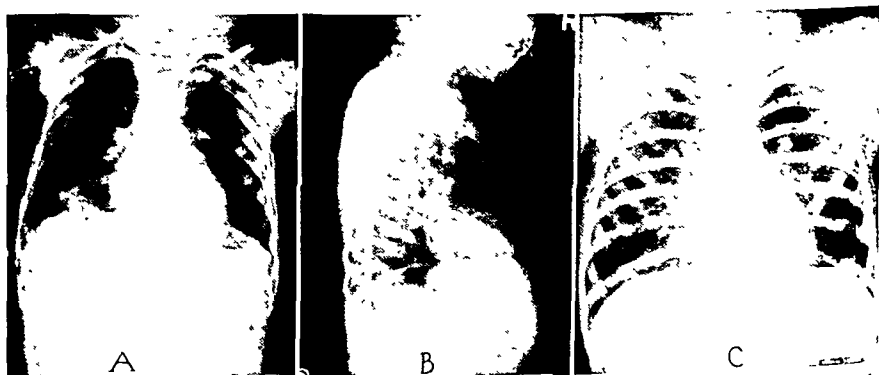


FIG. 3. A, anteroposterior chest film showing right lower lobe metastasis on March 31 1950. B, lateral chest x-ray locates metastasis in base anteriorly. C, normal anteroposterior chest film on August 15, 1951.

quickly disappeared. A chest film on September 15, 1951 (fig. 2, B) demonstrates the pulmonary fields still to be free of neoplasm. This represents a  $4\frac{1}{2}$  year survival.

*Case 2.* D. L. H. (137949) a  $2\frac{1}{2}$  year old white boy, had had a hard mass in his left flank for 10 days prior to hospital admission on September 9, 1949. The parents stated the child had no complaints. A large mass extending below the left iliac crest occupied the left abdomen. The blood studies and urinalysis were normal. The blood pressure was 110/60. Chest and long bone studies were normal. An excretory urogram was diagnostic of Wilms' tumor so cystoscopy was not employed. X-ray therapy was begun immediately over the left abdomen, delivering 2400 r to three ports over a period of 13 days. A transabdominal nephrectomy was carried out on the fourteenth day. Postoperative radiation was resumed shortly after surgery. A total of 2400 r was given to the left abdomen postoperatively. On March 9, 1950 a metastasis  $2\frac{1}{2}$  cm. in diameter was noted by chest x-ray in the right lung base (fig. 3, A and B). A total of 4300 r was delivered to both lung fields. Resolution of the neoplastic deposit was prompt

and on last follow-up study (fig. 3, *C*) the patient was free of demonstrable metastases. This is an 18 month survival dating from final x-ray therapy.

#### DISCUSSION

It is our feeling that success in the treatment of Wilms's tumor is a product of four factors. First, the early diagnosis by keen and enthusiastic practitioners is of prime importance. It has been shown repeatedly that success is inversely proportional to patient age. Second, aggressive therapeutic measures designed to bring the patient to nephrectomy at the earliest possible date compatible with complete removal of the tumor is desirable. This may envisage a long, short or no preoperative radiation period. Third, the transperitoneal nephrectomy or thoraco-abdominal nephrectomy if the tumor remains large with radiation, though difficult to support statistically, is the approach of choice in the majority of instances. Not only does it afford an early pedicle ligation, but also presents a wider field allowing exploration for abdominal metastases. Finally, routine postoperative radiation at the nephrectomy site and to any metastatic area will, in our opinion, reward the therapist.

#### SUMMARY

A series of 24 cases of Wilms's tumor is presented.

Histogenesis, symptomatology and diagnosis are discussed briefly.

The various forms of therapy are discussed in more detail.

A 2 year survival rate of 42.9 per cent was realized on those cases managed primarily by the Indiana University Medical Center.

A plea is made for early nephrectomy, using preoperative x-ray in the larger neoplasms to render them more readily operable.

Post-operative x-ray therapy to the operative site and to metastatic deposits is urged. Two case histories are appended to emphasize this policy.

The authors wish to express their appreciation for the continued support and co-operation of Dr. John A. Campbell, director of the Department of Radiology, Indiana University Medical Center.

#### ADDENDUM

Since submission of this paper for publication, all patients herein reported as living and well have been re-examined and continue free of metastases.

## ATTEMPTED DISINTEGRATION OF CALCULI BY ULTRASONIC VIBRATIONS

WILLIAM P. MULVANEY

The science of ultrasonics is less than forty years old. Its applications in industry and in the military have been extensively studied and employed. In spite of early investigation in Europe and more recently in this country, the medical aspects remain relatively unexplored.

Briefly, ultrasound waves are those which have a frequency higher than 17,000 vibrations per second. They are inaudible to the human ear. In the laboratory they are usually produced by a piezo-electric crystal. Such a crystal undergoes mechanical vibration and produces ultrasonic energy when opposite sides are subjected to an alternating current field. For production of ultrasound quartz and certain synthetic crystals are used with an electric radio-oscillator generating the current fields. Changing the energy source and the type or dimension of the crystals provides a variety of power with which one may study the effects of acoustic energy.

Any material with the property of elasticity can propagate ultrasonic waves. A liquid with a detergent is an efficient transmitting agent and is most suitable for experiment. The crystal is immersed in the liquid with the target for radiation placed at a proper distance for correct focusing.

The mechanical, thermal, chemical, biologic and physiologic effects of ultrasound have been summarized by Nelson, Herrick and Krusen.<sup>1</sup>

The phenomena associated with ultrasound are complex and varied. Emulsification, flocculation and dispersion of material may be produced by different frequencies. Physiologically disintegration of intracellular bodies and cytolysis have been caused by powerful ultrasonic energy.<sup>2, 3</sup> Bactericidal and virucidal effects have been studied in Europe and Japan. Ultrasound has been used for destroying larvae in malaria control projects. German clinicians<sup>4</sup> report superficial skin changes of hyperemia, edema and vesiculation in treating cases of sciatica, neuralgia and arthritis. They claim beneficial results. They found that frequencies lower than 500,000 cycles per second were more penetrating and less painful to the patient. By varying the energy output actual tissue damage can be caused. Lynn and Putman<sup>5</sup> produced lesions in the brains of animals by radiating through the intact skull. Gangrene of the scalp resulted. The effects followed the entire cone of transmission and were not limited to the focal point. Recently

Accepted for publication November 4, 1952.

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<sup>2</sup> Schmidt, T. O. and Uhlmeier, B.: The mechanism of the lethal effect of ultrasonic radiation. Proc. Soc. Exper. Biol. and Med., 27: 626, 1936.

<sup>3</sup> Lepeschkin, W. W. and Goldman, D. E.: Changes in the structure of cells on exposure to ultrasound. Nav. M. Research. Inst. Project. N. M. 004001. Rept. 3 (Jan. 6) 1949.

<sup>4</sup> Dittmar, Carl: Über die Wirkung von Ultraschallwellung auf tierische Tumoren. Strahlentherapie, 78: 217, 1948.

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interest in the treatment of malignancies has been intense. It has been shown that superficially located tumors may be destroyed by ultrasound. The potentiality of this type of therapy is still undetermined.

#### THE PROBLEM

An object in the radiation field of an ultrasonic crystal operating at high frequency shows no perceptible movement. There is the apparent paradox of acceleration without motion. The alternate compression and pulling apart of the particles in the field reaches a critical point at which the disruptive force exceeds the molecular attractive bond and the material is disintegrated. This is known as *cavitation*. The occurrence of *cavitation* effected by ultrasonic radiation makes theoretically reasonable an hypothesis that a calculus may be shattered by properly applied acoustic energy.

We envisage the disintegration of calculi to a particular size small enough to be irrigated from the bladder or other organ through an appropriate instrument.

The shortcomings of available lithotrites need not be enumerated here. Basically lithotrites have changed little from the primitive instruments used in early centuries. An efficient substitute would be desirable.

The impetus of war in developing improved electronic equipment has given us new and more powerful acoustic energy with which to work. The acquisition of synthetic crystals providing relatively tremendous energy provoked the present experimentation in spite of discouraging reports of similar work.

#### EQUIPMENT

Most investigators have used a quartz crystal mounted between two metal electrodes submerged in insulating oil. The oil provides a medium for transmission of the vibrations and an insulation for the high voltage electrodes. Such equipment utilizes about 2000 volts which makes its use potentially dangerous. Our early experiments were with a crystal of this type. It soon became apparent that the energy available was not sufficient for our purposes and the high voltage posed a practical disadvantage. Recently synthetic crystals have become available under the stimulus of sonar research. Our apparatus consisted of a barium tartrate crystal suspended in a water bath. We found that degassed water was the best medium of transmission and a container with a concave bottom the most satisfactory. An electric radio-oscillator generated the alternating current field. Most of our radiations were made at 8 to 9 amperes and produced frequencies of 440,000 cycles per second. These crystals provided extremely powerful ultrasonic energy.

#### METHOD

The first problem explored was the effect of properly focused ultrasonic waves of varying frequency acting directly on different calculi. A variety of hard and soft urinary and biliary calculi were used. They were suspended in wire cages held directly in the water bath and bombarded for multiple increments of 60 seconds each. The water medium became tepid and eventually warm during use. Heat production was found to enhance the power output of the crystal. From a clinical

standpoint a slowly circulating volume of irrigating fluid would be adequate for cooling. With 60 seconds of radiation small particles and granules on the surface of all calculi were displaced. This increased with prolonged exposure. The main architecture remained undisturbed, however, for periods up to 30 minutes. The softer phosphate and carbonate stones with more organic component were slightly more affected. German experimenters<sup>6</sup> have reported fracturing biliary calculi of mixed types after exposures of more than one hour. We were of the opinion that 30 minutes more than exceeded the bounds of practicality. It became apparent that the presently available equipment is incapable of disrupting calculi by direct exposure to acoustic trauma, and added nothing to the already existing methods available to the urologist.

It was noted that the surface of the stones in direct contact with the wire holders became more rapidly eroded. This was attributed to friction between the two

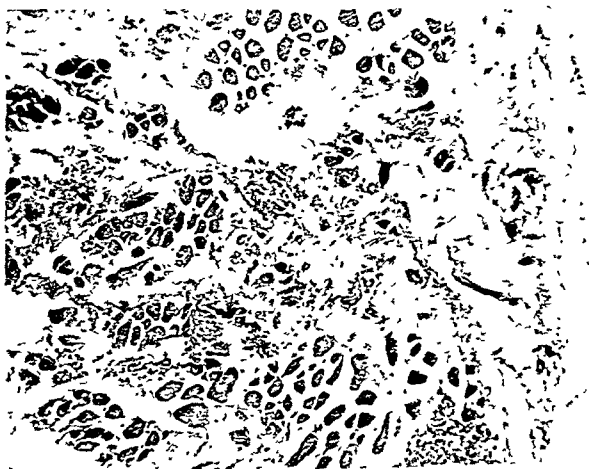


FIG. 1. Section of bladder wall radiated for 60 seconds at 440,000 cycles per second showing trauma which may be produced by direct exposure of muscle to powerful ultrasonic energy.

solid bodies vibrating in disharmony. It was speculated that an applicator of metal or other hard substance could be made to deliver acoustic energy to the calculus with better effect. Accordingly applicators or *buttons* were made of glass, aluminum and steel.

The proximal end was constructed in the shape of a disc with a concave collecting face. The distal activated end was gradually tapered to a point. These *buttons* were made in several variations of shape and material. All embodied the principle of collecting acoustic energy from the crystal at its focal point and delivering it to the stone through a tapered rod. Mechanical trauma was definite but limited to the small area of application. It was of insufficient magnitude to be of real use. Solids are not efficient transmitters of high frequency sound waves. Mercury is an excellent transmitter, however, and may be of value in delivering the acoustic energy through an instrument to the calculus.

<sup>6</sup> Berlinicke, M. L. and Schennetlén, F. Über beeinflussung von Gallensteinen durch Ultraschall in Vitro Vorläufige Mitteilung I Med. Univ. Klin. d. Charité Berlin Klin. Wschi., 21/22: 390, 1951.

The possibility of tissue damage has been considered. Mechanical trauma is produced in tissue by certain frequencies of ultrasound. This difficulty may be overcome by more accurate focusing of the waves with improved crystals or by using the principle of the *button* (fig. 1).

#### CONCLUSIONS

The experiments demonstrate that our present electronic equipment is not capable as yet of practical use in the disruption of urinary calculi. We believe the results are encouraging and presage effective methods in the not distant future. The project is soundly based on the theories involved. With the available apparatus calculi may be agitated to the point of partial disruption under clinically impracticable conditions. At the present rate of progress it may be hoped the infant science of ultrasonics will produce an ultrasonic device capable of disrupting urinary calculi.

#### ACKNOWLEDGMENTS

To Dr. Frederic E. B. Foley for his encouragement and advice; but mainly for his stimulation by example in bringing original and brilliant ideas to fulfillment.

To Dr. Otto Schmitt, Professor of Physics, University of Minnesota, for his technical teaching and help.

To the Lexington Foundation of Saint Paul, Minnesota, for providing the crystals used in the experiments.

*104 Union Central Bldg., Cincinnati, Ohio*



## COMPLICATIONS ARISING FROM TRANSURETHRAL MANIPULATION OF URETERAL CALCULI

JOSEPH H. IWANO AND R. CARL BUNTS

*From the Department of Urology, McGuire V. A. Hospital, Richmond, Va.*

Basically there are two methods of managing ureteral calculi by so-called conservative means. First, the ureter can be mechanically dilated. Second, the stone may be caught in an instrument and withdrawn. Examples of the first are dilatation by the use of multiple catheters and by the Dourmashkin rubber bag catheter. Examples of the second are the extraction by the various "stone baskets" and the looped catheters.

Councill introduced a ureteral stone extractor in 1926. Ferguson introduced his instrument in 1935, and Johnson in 1937. McKay's extractor, using silk thread instead of wire, was first used in 1930. As could be expected, certain complications have arisen following the widespread use of the various instruments. Rusche and Bacon reported among a series of 17 patients with ureteral injuries 3 cases in which the Johnson basket perforated or contributed to the perforation of the ureter. Councill in 1945 observed three ruptured ureters in a series of 504 cases. Included in this series was 1 patient with reflex anuria lasting 48 hours, two in whom phlebitis developed, and two others in whom septicemia was the complicating factor following the use of his instrument. Other complications in the use of instruments for stone manipulation have been on the whole ignored in the literature. Our report includes 9 patients who have suffered ureteral injury from all methods of transurethral manipulation, five occurring at our hospital since 1946 and four additional cases from elsewhere.

### COMPLICATIONS FROM THE USE OF STONE BASKETS

*Loss of parts of the instruments in the ureter.* Case 1: A 27 year old white man was admitted to McGuire V. A. Hospital with a small calculus in his left ureter at the ureterovesical junction. An attempt was made to extract the calculus with a Johnson stone basket. However, the basket became arrested at the ureterovesical junction. After a few minutes of manipulation the basket was recovered with the stone but without its filiform tip (fig. 1, A). Attempts to bypass the tip with another Johnson basket and ureteral catheters failed. Through a transvesical route the filiform tip was easily recovered.

Case 2: A 78 year old white man was admitted to another hospital with a calculus in his left lower ureter. A Johnson stone basket was passed up the ureter. Upon withdrawing the instrument the basket was found to have snapped off from its handle at the neck and was now lying in the ureter (fig. 1, B). At operation the basket with the stone was extracted. Following this harrowing experi-

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Read at annual meeting, Mid-Atlantic Section, American Urological Association, Roanoke, Va., March 13, 1952.

ence the physician was demonstrating to a colleague what had happened with another Johnson basket when the basket again snapped off completely, this time, fortunately, in his hand.

These 2 cases illustrate the importance of routinely checking one's equipment before its use. Before using the basket the operator should routinely tighten the tip and in manipulating the basket the instrument should always be turned in a clockwise manner.

*Use of the basket where the stone is too large or located high in the ureter.* Case 3: A 35 year old white man was transferred to McGuire V. A. Hospital from another hospital. He had a left ureteral calculus and attempts to extract it with a Councill basket had been unsuccessful. Following this procedure the left kidney had be-

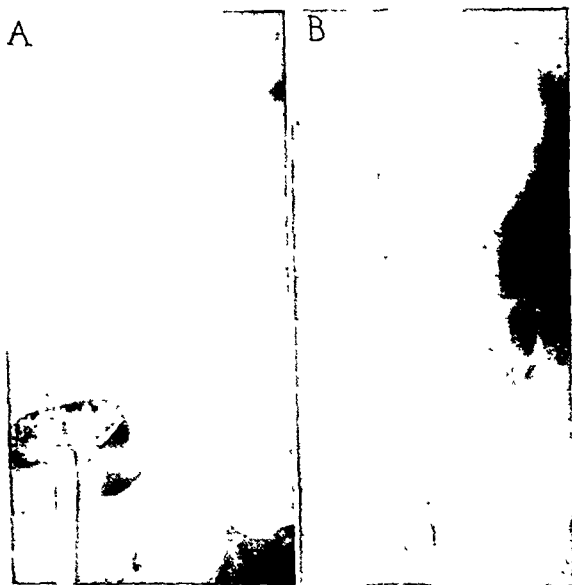


FIG. 1. A, filiform tip from Johnson ureteral stone basket "lost" in ureter. B, entire basket broken off from Johnson ureteral stone extractor.

come greatly enlarged and palpable, and excretory urograms revealed a non-functioning kidney. X-rays which had been taken during the attempted removal showed the basket with a rather large stone measuring 1 by 2 cm. in the middle third of the ureter with the tip of the basket almost in the area of the kidney pelvis (fig. 2). A ureterolithotomy was performed at our hospital using a trans-vesical approach. A fragmented stone impacted at the ureterovesical junction was removed. The ureteral orifice was gangrenous. He made a good recovery and postoperative x-rays taken 2 months later showed good function with some remaining caliectasis.

Two points are illustrated in this case. First, the stone was too large for extraction with a basket. Any stone larger than 0.5 cm. in diameter we regard with caution. A good rule is that of Thompson, as quoted by Emmett, who stated that two 5F catheters should easily pass the stone if a basket is to be

employed. Second, the instrument was passed too high up the ureter. The ureter, when entering the bony pelvis, follows the curve of the pelvis and the passage of a relatively stiff and large object as a stone basket through the pelvic ureter materially increases the chance of a perforation or rupture, especially since a portion of the ureter may already be weakened by infection. Also, the wires of the instrument in traversing the ureter traumatize the mucosa to some degree. Naturally, it is best to limit the trauma to a small segment rather than to have it extend the whole length of the ureter. We were rather dismayed to find in an otherwise excellent paper appearing recently in the *Journal of Urology* that the authors advocated the removal of stones from the upper ureter and the kidney pelvis with the Johnson stone basket.



FIG. 2. Council stone basket in ureter. Note how high instrument has been inserted (arrow points to end of tip). Ureter has been forcibly straightened out by high insertion. Note also wide separation of wires as compared with figure 1, B.

We would also like to comment on the relative merits of the Council and Johnson stone extractors. We have discontinued the use of the Council basket since the latter instruments have been made available. We believe that in comparison the Council basket is cumbersome and the separation of the wire strands causes extreme dilatation of the ureter. Compare figures 1, B and 2.

*Edema of the ureter following manipulation causing hydro-ureter and hydro-nephrosis.* Case 4: A 36 year old man was admitted to McGuire V. A. Hospital with a small calculus in his lower right ureter. This was removed by manipulation with a Johnson basket and an Ellik looped catheter. A ureteral catheter was left indwelling overnight and the patient discharged the following day. Five days later he returned complaining of pain in his right flank which had begun soon after he was discharged. Excretory urograms showed the right ureter dilated

down to the last few centimeters at which point the ureteral lumen appeared extremely constricted (fig. 3). On cystoscopy the ureteral meatus was found very edematous. Upon passing a catheter up the ureter the patient experienced immediate relief of pain. Urine from the kidney was cultured without growth of bacteria.

We have had a few other cases paralleling the aforementioned course. Because of such experiences we routinely leave an indwelling ureteral catheter for at least 24 hours. Ureteral meatotomy should be carried out in those cases in which there is stenosis at the ureteral meatus. We also believe that edema and trauma may be lessened if the procedure is limited to no more than three attempts (passage of the instrument) at any one sitting.

*Infection following manipulation.* Case 5: A 25 year old white man was admitted to McGuire V. A. Hospital with a stone in his right lower ureter. Attempts

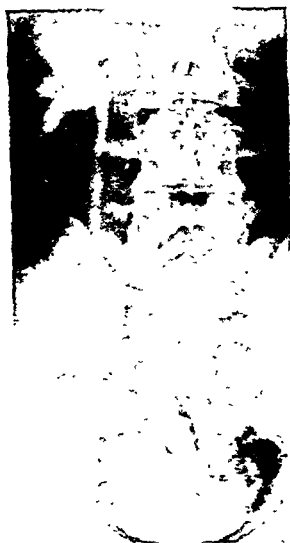


FIG. 3. Dilatation of ureter and kidney pelvis as result of spasm and edema in lower segment of ureter following instrumentation for calculus.

were made on two separate occasions to remove the stone with a Johnson basket without success. Following the second manipulation severe pyelonephritis developed followed by cortical abscess formation which necessitated pyelosotomy drainage.

This occurred before today's wide spectrum antibiotics were available and such cases should be relatively rare these days. As we believe it practically impossible to manipulate ureteral calculi without introducing some infection, we routinely administer some form of antibiotics before and after the procedure.

#### COMPLICATIONS FROM THE USE OF LOOPED CATHETERS

The looped catheter was introduced by Zeiss in 1937 and later modified by Wehrbein, Balkus, and Ellik. It has proved to be a valuable addition to the armamentarium of the urologist. At our hospital the looped catheter is sometimes

used for small calculi present in the upper two-thirds of the ureter. As in the use of stone baskets there are dangers in the use of the looped catheter. Ellik and Newton reported four ruptured ureters in a series of 104 patients with one nephrectomy being necessary.

*Rupture of ureter.* Case 6: A 29 year old white man was admitted to McGuire V. A. Hospital with a calculus in the upper third of the right ureter. An attempt was made to extract the calculus with an Ellik looped catheter. The catheter was soft so a wire stylet was used to stiffen it. It went past the stone with some difficulty. X-rays revealed the loop of the catheter to be lying outside of the ureter and attempts to pass catheters by the rupture failed (fig. 4). At operation it was found that the stone had almost eroded through the wall of the ureter, this being the point of rupture.



FIG. 4. Rupture of ureter by looped catheter

This case emphasizes the prime requisite of gentleness in manipulating stones. With the addition of a stylet enough rigidity was introduced to the catheter for it to tear through the weak spot.

At times we may hear one of our colleagues speak of "sweeping the ureter" with a loop for symptoms simulating a nonopaque stone. We believe such practice may be hazardous and that passing an ordinary catheter will give as much information as to the presence of a stone and is much less traumatic.

*Avulsion of ureteral mucous membrane.* Case 7: A 27 year old white woman in the first trimester of pregnancy was admitted to a local hospital with a calculus in the lower third of the right ureter. This was engaged by a looped catheter and the catheter was left in place with rubber band tension applied to it. At the end of 72 hours the loop was found to have pulled out through the urethra not only with the stone but also with the entire mucosa from the distal three centimeters of the ureter. A plastic repair of the ureter was performed but failed due to the splinting catheter being accidentally pulled out on the third day. Nephrostomy drainage was instituted but nephrectomy was eventually necessary after a normal delivery.

## COMPLICATIONS FROM THE USE OF DILATING INSTRUMENTS

*Rupture of ureter by a Dourmashkin bag catheter.* Dourmashkin reported some remarkable results using his metallic bougies and rubber bag catheter. Of 1253 cases treated he was successful in 1171, or 93.5 per cent. He encountered no ruptured ureters. We have not been so fortunate as we have used his rubber bag catheter in but a handful of patients and have had an accident. Recently Taylor also reported rupturing one ureter definitely and another probably with a Dourmashkin bag.



FIG. 5. A. Dourmashkin bag catheter in ureter. Catheter bag has 1 cc water in it and diameter is in excess of 1 cm. B. extravasation of contrast material from ureter caused by rupture of ureter by Dourmashkin bag catheter.

Case 8: A 25 year old white man was admitted to McGuire V. A. Hospital with a small calculus in the middle third of the left ureter. An attempt was made to dilate the ureter below the stone with a Dourmashkin bag catheter using the technique as described by him (fig. 5, A). However, during the procedure the ureter was ruptured to a degree necessitating surgical drainage (fig. 5, B).

Figure 6, A reveals the extreme dilatation caused by the catheter bag. By actual measurement the advocated 1 cc of water inflates the Dourmashkin bag to a diameter of over one centimeter. As we are instrumenting the ureter below the stone we are acutely dilating normal ureter from about 3 mm. to over 10 mm.

*Rupture of ureter by a ureteral bougie.* Case 9: A 30 year old white man was admitted to McGuire V. A. Hospital as a transfer from another hospital. A letter from his physician stated that he had been originally seen because of a

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*Rupture of ureter by a urethral bougie.* Case 9: A 30 year old white man was admitted to McGuire V. A. Hospital as a transfer from another hospital. A letter from his physician stated that he had been originally seen because of a



small calculus in the upper third of his right ureter. Attempts to dislodge it with an olive tip ureteral bougie had resulted in rupture of the ureter. When seen at our hospital he had a firm, tender mass in the right lower quadrant of his abdomen. At operation 12 hours after admission a large abscess along the right psoas muscle was evacuated. Neither the actual point of extravasation nor the stone could be located. The patient did well postoperatively. X-rays showed an extra-ureteral density below the lower pole of the right kidney which was thought to represent the stone which had escaped through the perforation. At a subsequent date the patient passed another stone which blocked the ureter causing extravasation presumably at the former site of rupture and this necessitated nephrectomy.

In retrospect, after the first attempt at catheterization failed, operative removal of the calculus was in order. "Pseudo" conservatism in this case as well as in case 6 resulted in the sacrifice of a good kidney.

#### COMMENT AND SUMMARY

Although the majority of ureteral calculi may be removed successfully without complications transurethrally, the foregoing cases demonstrate that complications do occur only too frequently not only to the neophyte but to the experienced urologist, as these patients were treated by 7 men with experience in urology varying from resident training to 30 years of practice. We do not condemn the use of ureteral stone instruments. Members of the urologic staff at our hospital have removed scores of calculi transurethrally over the years without complications. We do say, however, on the basis of the review of our records, instead of being a conservative procedure the transurethral manipulation of ureteral calculi proves to be the more radical procedure in some cases. This we believe especially true in dealing with stones in the upper ureter.

In summary let us again set forth the precautions to be carried out in instrumental stone manipulation:

Gentleness is an absolute prerequisite in manipulating ureteral calculi.

All instruments should be checked before use; the filiform tip should be routinely tightened and the instrument should be turned only in a clockwise manner.

Stone baskets should not be used when the calculus is much larger than 0.5 cm. in diameter or if it is located above the true bony pelvis.

Stenotic ureteral meatuses should be dilated or incised when indicated.

Cumbersome stone extractors that cause extreme dilatation of the ureter should not be used.

In most cases it is wise to leave an indwelling ureteral catheter from 24 to 48 hours following manipulation with a stone basket.

Antibiotics should be administered before and after manipulation.

#### CONCLUSIONS

Complications resulting from the transurethral manipulation of ureteral calculi in 9 patients have been reported.

Certain precautions that should be observed have been expressed.

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## URETERAL STONE IN A CHILD: EXTRACTION BY LOOPED CATHETER

MILO ELLIK AND JOHN GETZ

*From the Department of Urology, Los Angeles County Harbor General Hospital and the University of California at Los Angeles School of Medicine, Los Angeles, Calif*

Urinary calculi are not too common in childhood and an impacted ureteral stone is an exceedingly rare pediatric problem. Although the latter is frequently solved by cystoscopic aid in adults, forceful manipulation is relatively unknown in juveniles. Anatomical limitations compounded upon the limited capacity of infant cystoscopes have always established an attitude of procrastination in even the most venturesome. Those who disfavor forceful cystoscopic extraction of ureteral calculi at any time would of course designate it as foolhardy in childhood. Pediatric urology has not embraced such manipulation to date; Campbell states that no similar case has come to his attention and therefore it would appear that forceful extraction of ureteral stone in the very young is without precedent.

Among recognized ureteral stone extracting devices, the looped catheter is the smallest, the most pliable and the only one accommodated by infant cystoscopes. The latter fact makes its use conceivable in childhood. The authors, when recently confronted by an impacted calculus in a ten year old boy, elected to venture forceful manipulation with this instrument. It had been shown that the child's urethra would barely admit a McCarthy cystoscope of the infant variety. It was well known that the ureter of a child frequently admits a 5F ureteral catheter and that the looped catheter being of the latter size would be admitted through the lumen of the infant cystoscope. It remained only to determine whether the formation of the loop and the forces applied to it would be tolerated both by the child and his immature structures. It is believed that the following case report represents the initial instance of such procedure performed under similar circumstances.

### CASE REPORT

J. F., a boy of barely 10 years of age and of perhaps less than average size, entered the hospital 2 days after having incurred a head injury at play in the school yard. Sporadic nausea, vomiting and abdominal pain had followed the injury. Examination revealed a thin, pale, disoriented child appearing moderately ill. His temperature, pulse and blood pressure were normal. The only evidence of external violence was right peri-orbital ecchymosis with edema and some subconjunctival hemorrhage. Epigastric tenderness and generalized abdominal guarding were noted. The deep tendon reflexes were hyperactive bilaterally but no pathological reflexes were present. Urine was normal microscopically and chemically. Blood leukocytes were reported as 18,000 with 77 per cent polymorphonuclears. Skull roentgenograms, cerebrospinal fluid findings and blood urea nitrogen were all negative.

Accepted for publication November 4, 1952

Gross bloody urine appeared on the third hospital day and left costovertebral angle tenderness became noticeable. Urological consultation was requested forthwith and a preliminary scout film of the abdomen revealed a small density, 1 by 0.5 cm. in the region of the extreme lower left ureter. Excretory urography demonstrated a non-functioning left kidney (fig. 1, A). The upper right urinary tract and bladder area appeared to be normal. Left costovertebral and left flank pains became somewhat more intense. Cystoscopy with retrograde pyelography was performed on the fifth hospital day and verified a stone in the lower left ureter (fig. 1, B). A 4F ureteral catheter met resistance at the juxtavesical end of the left ureter but could finally be insinuated past the calculus and inserted all the way to the left renal pelvis (fig. 1, C). Only 4 cc of residual urine was aspirated from this cavity and ureteropyelograms showed moderate dilatation of both above the level of the stone. This catheter was left indwelling for dilatation and drainage over a 4-day period. Three days after the removal of this catheter,



FIG. 1

the stone had not progressed in descent so another catheter of the same size was again inserted past the stone and left indwelling for similar management over a 2-day period. The stone still did not progress so this type of conservative management was abandoned and the looped catheter extractor similarly inserted with great care. This instrument passed by the stone with ease and its loop closed within the renal pelvis without event. The loop was immediately withdrawn down the ureter until the tip of the loop first made contact with the stone and at this point all traction or manipulation was discontinued. The patient was returned to his bed to await spontaneous encirclement and his toleration of the indwelling device evaluated. Had the latter been poor, ureterolithotomy was contemplated. He tolerated it well, and 24 hours after its placement x-rays showed very satisfactory engagement of the stone within the loop (fig. 2, A). Traction upon the stone was instituted several times daily thereafter and the calculus came away still clasped within the loop seven days later (fig. 2, B). The instrument had apparently kept an uninterrupted purchase upon the stone throughout this

period. No greater than 2 pounds of pull was used at any time and usually much less. The child resumed normal, comfortable ambulation and play during his waking day and slept peacefully at night. He voided freely about the protruding instrument. He required no anesthesia or analgesia at the time of traction. He would climb, without coercion, into his hospital bed at any time for a reasonably short period of traction and tolerated pull upon the instrument without more

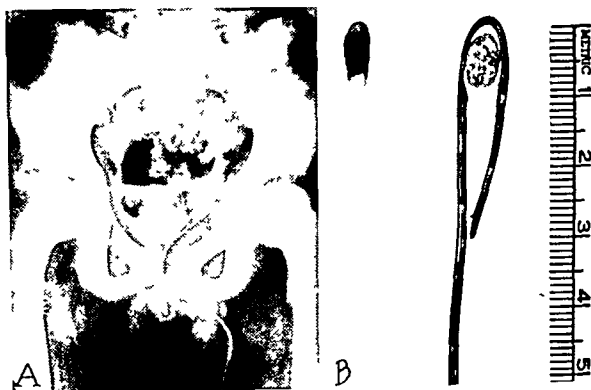


FIG. 2



FIG. 3

than some whimpering and grimaces. The calculus measured 8 by 5 mm., which was slightly smaller than the x-ray measurements would have indicated. It proved to be very hard, irregular and its chemical analysis was reported as oxalate.

#### COMMENT

Interesting phases of this unusual case included the fact that at no time until the day of actual extraction was there any febrile reaction. Temperature rose to

103.4F just after the stone's exodus. Antibiotics were then instituted for the first time and temperature reactions leveled off to normal during the next four days. The time honored conservative indwelling catheter was given an ample opportunity for dilatation and undoubtedly aided in the ultimate passage of the looped device, but the stone was apparently too large and irregular to pass spontaneously. The seven day traction period attested to formidable disparity between size of stone and the segment of ureter distal to it. A compilation of total hospital days necessitated for the numerous manipulations compared with those theoretically needed for ureterolithotomy, might speak favorably for the latter on this basis alone. For the sake of standard investigation, blood chemistry determinations along with blood and urine calcium phosphorus levels were recorded and were normal. Urine cultures showed *E. coli* and *Staph. aureus* on one occasion, others being bloody but sterile. Excretory urography one week after the stone had been removed showed good function of both kidneys and a marked recession of the ureteropelvic dilatation on the left (fig. 3). A most striking feature was the child's stoical tolerance of the device. The structures involved not only accommodated the instrument readily, but withstood the force applied without event. Of course, the case leads to conjecture as to the applicability of such a procedure in even younger children. The looped catheter can be made at 4F and could conceivably be reduced to 3F should it be so desired. The sum of all these factors, it is hoped, will inspire future efforts in this direction by those who meet the same problem.

#### CONCLUSIONS

It is believed that this case report represents the initial one of its kind and that cystoscopic extraction of ureteral calculi in children has thus been shown feasible.

Because the looped catheter extractor is standard at size 5F and could conceivably be made smaller, it is the only and logical choice for doing such a procedure in a child.

Perhaps children younger than 10 years would tolerate a similar procedure; it is hoped that this case will recall such possibility in the future.

117 E. 8th St., Long Beach 13, Calif. (M. E.)

3875 Wilshire Blvd., Los Angeles 5, Calif. (J. G.)

#### REFERENCES

- CAMPBELL, M. Clinical Pediatric Urology. Philadelphia W B Saunders Co., 1951
- LELIK, M. Stones in the ureter, their extraction by looped catheter. *J Urol*, 57: 473-478, 1947
- LELIK, M. The looped catheter ureteral stone extractor. Perplexities in its construction and use. *J Urol*, 61: 351-358, 1949
- LELIK, M. AND NEWTON, L. A. Ureteral calculi. Experiences in looped catheter management. *J Urol*, 65: 532-539, 1951

period. No greater than 2 pounds of pull was used at any time and usually much less. The child resumed normal, comfortable ambulation and play during his waking day and slept peacefully at night. He voided freely about the protruding instrument. He required no anesthesia or analgesia at the time of traction. He would climb, without coercion, into his hospital bed at any time for a reasonably short period of traction and tolerated pull upon the instrument without more



FIG. 2



FIG. 3

than some whimpering and grimaces. The calculus measured 8 by 5 mm., which was slightly smaller than the x-ray measurements would have indicated. It proved to be very hard, irregular and its chemical analysis was reported as oxalate.

#### COMMENT

Interesting phases of this unusual case included the fact that at no time until the day of actual extraction was there any febrile reaction. Temperature rose to

103.4F just after the stone's exodus. Antibiotics were then instituted for the first time and temperature reactions leveled off to normal during the next four days. The time honored conservative indwelling catheter was given an ample opportunity for dilatation and undoubtedly aided in the ultimate passage of the looped device, but the stone was apparently too large and irregular to pass spontaneously. The seven day traction period attested to formidable disparity between size of stone and the segment of ureter distal to it. A compilation of total hospital days necessitated for the numerous manipulations compared with those theoretically needed for ureterolithotomy, might speak favorably for the latter on this basis alone. For the sake of standard investigation, blood chemistry determinations along with blood and urine calcium phosphorus levels were recorded and were normal. Urine cultures showed *E. coli* and *Staph. aureus* on one occasion, others being bloody but sterile. Excretory urography one week after the stone had been removed showed good function of both kidneys and a marked recession of the ureteropelvic dilatation on the left (fig. 3). A most striking feature was the child's stoical tolerance of the device. The structures involved not only accommodated the instrument readily, but withstood the force applied without event. Of course, the case leads to conjecture as to the applicability of such a procedure in even younger children. The looped catheter can be made at 4F and could conceivably be reduced to 3F should it be so desired. The sum of all these factors, it is hoped, will inspire future efforts in this direction by those who meet the same problem.

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LELLIK, M. AND NEWTON, L. A. Ureteral calculi. Experiences in looped catheter management *J. Urol.*, **65**: 332-339, 1951.



## PARAPLEGIA DUE TO VERTEBRAL METASTASIS OF PROSTATIC CARCINOMA: CASE REPORT

GEORGE K. KAWAICHI AND RICHARD D. RIDER

*From Veterans Administration Center, Wichita, Kans.*

Paraplegia caused by metastatic lesions of the vertebra from carcinoma of the prostate is uncommon. Roberts and Kuehn<sup>1</sup> in their review of recent literature found only seven reported cases of paraplegia from osseous metastases of prostatic carcinoma and cited a case with autopsy findings.

Edelman<sup>2</sup> reported a case of paraplegia secondary to metastatic prostatic carcinoma treated with stilbestrol. A case was recorded by Huggins<sup>3</sup> in which the paraplegia was relieved by bilateral orchiectomy. Another case from the records of the Massachusetts General Hospital<sup>4</sup> was treated by laminectomy.

A case of paraplegia due to vertebral metastasis of a prostatic carcinoma diagnosed by biopsy and the metastasis proved by surgery and necropsy constitutes the basis for this report.

### CASE REPORT

R. A. C., a 51 year old white man, was admitted to the hospital on February 16, 1949, complaining of difficulty in urination for 6 months. He had one episode of urinary retention requiring catheterization before entering the hospital. He also had nocturia 1 to 2 times and perineal pain for about 2 years.

Past history revealed no cancer in the family. He had mumps with orchitis on the left at the age of 21 and a chancre in 1920 with treatments.

Physical examination was normal except for a moderate atrophy of the left testicle. Rectal examination revealed an anterior thrombosed hemorrhoid. The prostate was enlarged, about grade 2, nontender, very firm, nodular and fixed. The residual urine was approximately 100 cc. Examination of the lower extremities revealed bilateral varicose veins with stasis dermatitis.

The red blood count was 4,350,000 with 15 gm. hemoglobin, the white blood count 7,250 with 76 per cent neutrophils. The blood urea nitrogen was 13 mg. per cent. The Kahn test was negative. Serum acid phosphatase was 0.3 Bodansky units. X-ray of the chest was normal. Excretory urography showed no abnormalities. X-ray of the spine and pelvis revealed no evidence of metastases. Cystoscopic examination showed normal bladder mucosa, with a grade 2 enlargement of the median and lateral lobes of the prostate.

Bilateral vasectomy was done on February 28, 1949, followed by a transurethral prostatic resection. Biopsy revealed adenocarcinoma of the prostate. The patient was placed on stilbestrol therapy and was advised to have orchiectomy, but refused. The patient was discharged on stilbestrol therapy and told to return for a recheck.

On August 2, 1949, serum acid phosphatase was 0.5 Bodansky units. How-

Accepted for publication July 30, 1952.

<sup>1</sup> Roberts, R. R. and Kuehn, C. A.: *Urol. & Cutan. Rev.*, **55**: 388, 1951.

<sup>2</sup> Edelman, I. S.: *Ann. Int. Med.*, **31**: 1098, 1949.

<sup>3</sup> Huggins, C.: *J. A. M. A.*, **131**: 576, 1946.

<sup>4</sup> *New Eng. J. Med.*, **237**: 878, 1947.

ever, the blood Kahn test was 4 plus with 128 quantitative units. Spinal fluid examination was negative. X-rays of the spine and pelvis were negative. He was continued on stilbestrol and was also given a course of penicillin, and was then discharged.

He returned to the hospital on December 16, 1950, with a backache. X-rays of the spine and pelvis were negative, and he was advised to continue stilbestrol.

The patient was re-admitted on March 5, 1951, complaining of progressive pain in the back radiating down to the left knee. X-rays of the spine revealed a metastatic lesion involving the body of the second lumbar vertebra (fig. 1). Serum acid phosphatase was 3.6 Bodansky units. Stilbestrol was continued and a bilateral orchiectomy was done on March 14, 1951. He also had bilateral

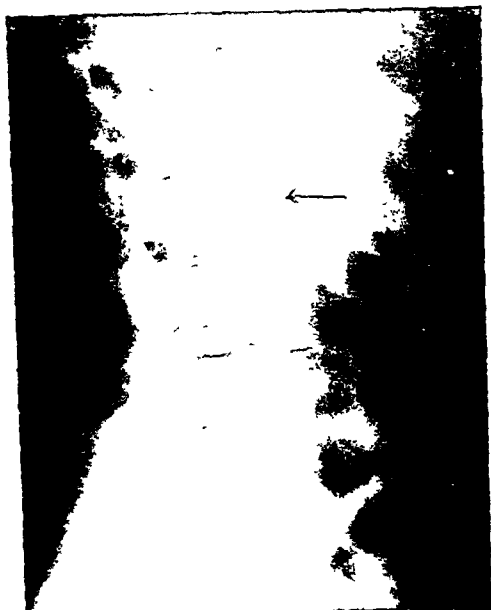


FIG. 1. X-ray of spine showing metastatic carcinoma of second lumbar vertebra

saphenous vein ligation for the varicose veins which became symptomatic. A Taylor back brace was advised and fitted by the orthopedic department before the patient was discharged.

He was again re-admitted to the hospital on June 8, 1951, still complaining of a backache with pain radiating down both legs as well as girdle pains which radiated around the lower chest and upper abdomen. Examination revealed slightly tender, hypertrophied breasts with dark nipples. Slight tenderness was elicited along the lumbar spine. The reflexes were normal. The serum acid phosphatase was now 6.4 Bodansky units. Kahn test was still strongly positive. X-ray of the chest was negative. X-ray of the spine showed continued destruction of the second lumbar vertebra. The patient was then started on a course of deep X-ray therapy to the metastatic lesion of the spine on June 13, 1951. Seven days later he began to complain of numbness and weakness of both legs and was soon unable to walk. The sensory loss gradually moved up to the costal margins.

Urinary retention developed and necessitated an indwelling catheter. X-rays taken on July 12, 1951 revealed absence of the pedicles of the sixth thoracic vertebra and a slight increase in density of the second lumbar vertebra.

The patient was seen by a neurosurgeon on July 13, 1951, who advised a decompression laminectomy which was performed on July 20, 1951. At operation, laminectomy was done bilaterally on the fifth, sixth and seventh thoracic vertebrae. There was found to be definite pressure on the spinal cord, caused by the infiltrative lesion of the sixth thoracic vertebra producing a constricting area at that level. This was relieved by the laminectomy. No infiltrative lesions were seen or palpated on the cord. Biopsy of the bone removed by laminectomy of the sixth thoracic vertebra showed metastatic carcinoma. The patient's condi-



FIG. 2. Section of sixth thoracic vertebra removed at autopsy shows metastatic carcinoma

tion remained critical for several days but gradually improved with good healing of the laminectomy wound. There was gradual return of sensation to about the level of the pubis, and the patient was able to move the thighs slightly. He was started on physiotherapy to the lower extremities to keep the joints active. However, there was no further recovery of the lower extremities and the patient gradually became worse and expired on October 5, 1951.

Autopsy findings (courtesy of Dr. Richard Cray): The heart weighed 500 gm. and showed myocardial hypertrophy of the left ventricle. The lungs were normal except for a small area of atelectasis in the lower right lobe. The spleen weighed 110 gm. and revealed hemochromatosis. The right kidney weighed 200 gm. and the left 260 gm. There was bilateral chronic interstitial nephritis. The urinary

bladder was normal. The prostate was small and slightly firm, and measured approximately 4 by 4 by 3.5 cm. Cut surface showed a firm, gray stroma without glandular appearance. The stroma was fibrous with occasional ducts and acini. There were large areas of infiltration with polygonal or cuboidal epithelial cells showing poorly defined borders. A small amount of basophilic cytoplasm and fairly regular round vesicular nuclei were seen. The cells formed irregular solid groups and many giant cells were present. A large amount of intracellular bright yellow pigment was present. The cells infiltrated about nerves. The breasts showed bilateral gynecomastia. Sections of the sixth thoracic vertebral body revealed areas of widely spaced and thickened trabeculae separated by loose fibrous tissue. The trabeculae were closely spaced and surrounded by osteoblasts. In some of these areas, small groups of neoplasm were present. In other areas, the trabeculae were extremely dense, wide and closely spaced, and showed large areas of necrosis (fig. 2). Diagnosis: Adenocarcinoma of the prostate with metastases to the thoracic and lumbar vertebrae.

#### DISCUSSION

As suggested by Roberts and Kuehn, the exact mechanism producing the paraplegia should be investigated. In this case there was definite pressure on the spinal cord from the infiltrative lesion of the vertebra as found by the neurosurgeon at the time of surgery. A definite constricting area was noted which was relieved by laminectomy. No lesions were seen or palpated in the cord. It is regretted that no spinal cord tissue was obtainable for microscopic examination at necropsy.

The possibility of a syphilitic lesion suggested by the positive serology was ruled out by the negative spinal fluid studies and the biopsy of the vertebra.

Although cases have been reported where the paraplegia was relieved by large doses of stilbestrol or orchiectomy, we believe that most of the cases are results of mechanical compression, and as such should be treated by laminectomy.

In the case cited in the records of the Massachusetts General Hospital, treated by laminectomy, complete recovery resulted. In this case the laminectomy was delayed but even then there was partial recovery. Of course, these patients should also have the benefit of estrogens and orchiectomy. Most patients who have vertebral metastasis from carcinoma of the prostate will already have had estrogen therapy and or orchiectomy, so that laminectomy will be the last resort. We strongly believe that all cases of paraplegia due to vertebral metastasis should have laminectomy as soon as the diagnosis is made. Even though these cases are apparently hopeless, it would be much better to attempt to relieve them of the paraplegia than to have a lingering bed-fast patient.

#### SUMMARY

A case of paraplegia due to vertebral metastasis of a prostatic carcinoma is presented.

The prostatic carcinoma was diagnosed by biopsy and the metastasis confirmed by surgery and necropsy.

Paraplegia was caused by cord compression secondary to metastasis to the sixth thoracic vertebra, as seen at operation.

## ACTH IN RADIATION CYSTITIS

LESTER PERSKY AND GEORGE AUSTEN JR.

*From the Department of Surgery, Urological Service, Western Reserve University School of Medicine, and University Hospitals, Cleveland, Ohio*

Injury to the bladder secondary to radiation therapy for malignancy of the female generative organs is now recognized as a not infrequent occurrence. Although occasional reports of a few cases with vesical damage so produced had appeared previously, it was Dean, in 1927, who first clearly indicated the true nature of these lesions.<sup>1</sup> Watson, Herger and Sauer in 1947 reported an incidence of both early and delayed reactions of nearly 3 per cent in almost 6,000 patients.<sup>2</sup> The incidence in other reported series closely parallels this figure.<sup>3</sup> However, these statistics probably do not denote the true incidence of late radiation reactions in the bladder. An appreciable proportion of patients with malignant disease of the uterus die within the first year following treatment and before vesical injury may become manifest. Also, it is more than likely that a number of patients treated have such bladder lesions which remain undiscovered for various reasons. And finally, it should be remembered that a certain number of patients treated during the last years of any given period of study can be expected to develop reactions at some future date. Thus, it is probable that the actual incidence of this type of bladder injury is considerably greater than is suggested by published reports.

Injuries to the bladder resulting from radiation treatment of uterine malignancy are in general of two types, the acute or early reaction and the late or "delayed" reaction. The acute radiation change develops usually secondary to external radiation, either during or shortly after such treatment, and is characterized histologically by a picture of acute inflammation involving mucosa and submucosa. It is the result of an acute epithelialitis involving the entire bladder wall, with changes comparable to the acute skin changes which may develop during or following external radiation therapy. Acute radiation reactions in the bladder apparently occur less frequently than the delayed reactions, and the majority of them heal rather promptly with or without nonspecific therapy, and with few complications.

However, it is the late radiation damage which is of particular interest in the present discussion. In contrast to the early or acute radiation injury, the delayed radiation reaction is generally considered to be invariably due to preceding radium application; and it may take some time, from one to as long as 8-10 years or more in occasional instances, before symptoms and signs manifest themselves.

The ACTH used in this study was obtained from Dr. Hymer Friedell, Director of Radiology, Western Reserve University School of Medicine, through the courtesy of Armour Laboratories, Chicago.

Accepted for publication November 4, 1952.

<sup>1</sup> Dean, A. L.: Ulceration of urinary bladder as late effect of radium applications to uterus. *J.A.M.A.*, 89: 1121, 1927.

<sup>2</sup> Watson, E. M., Herger, C. C. and Sauer, H. R.: Irradiation reactions in the bladder. *J. Urol.*, 57: 1038, 1947.

<sup>3</sup> Dean, A. L. and Slaughter, D. P.: Bladder injury subsequent to irradiation of uterus. *J. Urol.*, 46: 917, 1941.

The lesions of this type of reaction occur in a more localized portion of the bladder, principally the lower posterior wall and floor, and are the result of an endarteritis which may lead to complete local ischemia and necrosis of the area involved. The microscopic picture is one of fibrosis, round cell infiltration, edema and usually some increased surface vascularity. Unless damage is irreversible, healing will eventually occur in over 75 per cent of these cases.

There are, on the other hand, a certain percentage of patients with late, or delayed radiation reactions who develop encrusted ulcers, vesicovaginal fistulas, and/or embarrassment of the upper urinary tract.<sup>4-7</sup> The latter complication is a result of obstruction of the lower third of one or both ureters secondary to either perivesical fibrosis due to excessive radiation or scarring and stenosis of the ureteral orifice due to radiation damage to the bladder itself. In addition, before resolution of the injury takes place, periods of time may have elapsed varying from 6 months to upwards of 6 years or more,<sup>2</sup> with dysuria, frequency, nocturia and bleeding plaguing both patient and physician. In an effort to alleviate these symptoms and to eliminate some of the later complications, it seemed worthwhile to give ACTH a clinical test.

The possibility that this agent might be effective was suggested by several facts. Since the effect of radiation upon the bladder is primarily manifest in the mucous membrane and submucosa,<sup>8</sup> and since ACTH has been effective in diseases affecting the mucosa of other organs,<sup>6-7</sup> it was hoped that the pathological process could be reversed at an early stage. In the second place, it was hoped that the later scarring and fibrosis could be prevented, because of the known inhibitory effect of ACTH upon fibroblastic activity.<sup>6</sup> For these reasons, and because of the reported clinical effectiveness of the drug in the treatment of interstitial cystitis,<sup>10</sup> a disorder with somewhat similar symptomatology, this study was undertaken.

#### METHOD AND DOSAGE

The drug was administered intravenously to the first two patients because of its known greater potency by this route.<sup>11</sup> The third patient was treated by intermittent intramuscular injection. Preliminary studies prior to therapy included a complete blood count, complete examination and culture of the urine, eosino-

<sup>4</sup> Colby, F. H. Urinary tract complications from uterine cancer. *New Eng. J. Med.*, 209: 231, 1933.

<sup>5</sup> Everett, H. S. The effect of carcinoma of the cervix uteri and its treatment upon the urinary tract. *Am. J. Obst. & Gynec.* 33:889, 1939.

<sup>6</sup> Gray, S. J., Reifstein, R. W., Benson, J. A. and Young, J. C. G. Treatment of ulcerative colitis and regional enteritis with ACTH. *Arch. Int. Med.* 87:646, 1951.

<sup>7</sup> Karstner, J. B. and Palmer, W. L. ACTH in chronic ulcerative colitis, observations in 40 patients. *J. A. M. A.*, 147: 541, 1951.

<sup>8</sup> Loeb, O. S. and Kirwin, T. J. *Clinical Urology*. Baltimore: Williams and Williams Co., 1944.

<sup>9</sup> Ragan, C., Howes, L. L., Plotz, C. M., Meyer, K. and Blunt, J. W. Effect of cortisone on production of granuloma tissue in rabbit. *Proc. Soc. Exper. Biol. & Med.*, 72: 718-721, 1949.

<sup>10</sup> Weaver, R. G. and Tyler, F. H. The use of ACTH in interstitial cystitis. *Proc. 2nd Ann. ACTH Confer.* 2, 507 (1951) Blakiston Co., N. Y.

<sup>11</sup> Johnson, A. M., Stewart, P. B. and Beaumont, G. L. ACTH by intravenous infusion. *J. Urol.* 1: 120, 1950.

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However, it is the late radiation damage which is of particular interest in the present discussion. In contrast to the early or acute radiation injury, the delayed radiation reaction is generally considered to be invariably one occurring at a medium application and it may take some time, from one to as long as 5-10 years or more in occasional instances, before symptoms and signs manifest themselves.

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Accepted for publication November 4, 1952.

<sup>1</sup> Deane, A. L.: Ulceration of urinary bladder as late effect of radium application. *Br. J. Urol.* 1: 111-112, 1927.

<sup>2</sup> Watson, E. M., Harger, C. C. and Sauer, H. R.: Irradiation reactions in the bladder. *J. Urol.* 57: 1038, 1947.

<sup>3</sup> Deane, A. L. and Stoddard, D. P.: Bladder injury after radium therapy. *Br. J. Urol.* 45: 47, 1941.

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<sup>5</sup> Everett, H. S. The effect of carcinoma of the cervix uteri and its treatment upon the urinary tract. *Am J Obst & Gynec*, 38: 889, 1939.

<sup>6</sup> Gray, S. J., Reifstein, R. W., Benson, J. A. and Young, J. C. G. Treatment of ulcerative colitis and regional enteritis with ACTH. *Arch Int Med*, 87: 646, 1951.

<sup>7</sup> Kirsner, J. B. and Palmer, W. L. ACTH in chronic ulcerative colitis, observations in 40 patients. *JAMA*, 147: 541, 1951.

<sup>8</sup> Lowrey, O. S. and Kirwin, T. J. *Clinical Urology*. Baltimore: Williams and Wilkins Co., 1944.

<sup>9</sup> Rigau, C., Howes, E. L., Plotz, C. M., Meyer, K. and Blunt, J. W. Effect of cortisone on production of granulation tissue in rabbit. *Proc Soc Exper. Biol. & Med*, 72: 718-721, 1949.

<sup>10</sup> Weaver, R. G. and Tyler, F. H. The use of ACTH in interstitial cystitis. *Proc 2nd Clin ACTH Confer*, 2, 507 (1951) Blakiston Co., N. Y.

<sup>11</sup> Jelliffe, A. M., Stewart, P. B. and Beaumont, G. E. ACTH by intravenous infusion. *Lancet* 1: 1260, 1950.



phile counts,<sup>12</sup> serum Na and K levels, determination of the fasting blood sugar, and daily blood pressures.<sup>13</sup> Chemistries and eosinophile counts were repeated during and after treatment. All patients were placed on a low salt diet and were given supplementary potassium, 1 gm. 3 times daily. Cystoscopy was carried out prior to therapy, immediately after therapy and whenever indicated after termination of treatment. Whenever feasible, biopsy was taken before and after treatment. Intravenous dosage was 20 mg. daily for 10 days, the drug being administered in 1 liter of 5 per cent dextrose in water over a 6-8 hour period. The second patient had an abbreviated and incomplete course because of the appear-

TABLE 1. *Case summaries*

| CASE NO. | HOSPITAL NO.                       | AGE AT ACTH RX. | PRIMARY DISEASE                                    | X-RAY & RADIUM DOSAGE               | INTERVAL BEFORE RADIATION CYSTITIS | SYMPTOMS                                                              | ACTH DOSAGE |
|----------|------------------------------------|-----------------|----------------------------------------------------|-------------------------------------|------------------------------------|-----------------------------------------------------------------------|-------------|
| I        | 191593<br>UH                       | 60              | Squamous cell ca. of cervix, stage III             | 3577 mgh. radium, 3000 r-x-ray      | 10 yrs.                            | Urgency, frequency, nocturia, dysuria, and hematuria 3 yrs. duration  | 200 mg. IV  |
| II       | 604-055<br>UH                      | 37              | Undifferent. ca. of cervix, stage II               | 5,940 mgh. radium, 3049 r-x-ray     | 6 Mos.                             | Urgency, frequency, dysuria, hematuria 5 mos. duration                | 120 mg. IV  |
| III      | 277-181<br>UH<br>61652<br>Fairview | 37              | Poorly differentiated squamous cell ca. stage I B+ | 3775 2 mgh. of radium, 3672 r-x-ray | 3½ yrs.                            | Hematuria, dysuria, nocturia, frequency and urgency 1 week's duration | 1160 mg. IM |

\* Patient of Dr. Wm. L. Huffman, under whose management treatment was carried out.

TABLE 2. *Immediate results of treatment*

| CASE | DYSURIA |      | NOCTURIA |      | CAPACITY (CC.) |      | CYSTOSCOPY                            | BIOPSY             |
|------|---------|------|----------|------|----------------|------|---------------------------------------|--------------------|
|      | Pre     | Post | Pre      | Post | Pre            | Post |                                       |                    |
| I    | ++++    | 0    | 10-12    | 1-2  | 100            | 300  | Decreased area of ulceration          | Radiation cystitis |
| II   | ++++    | 0    | 8-10     | 0-1  | 150            | 300  | No change                             | Radiation cystitis |
| III  | ++++    | 0    | 3-4      | 0    | 150            | 400  | Slight decrease in area of ulceration | Chronic cystitis   |

ance of mental depression and agitation. Intermittent intramuscular dosage was 20 mg. every 4 hours for ten days.

## RESULTS

The agent to date has been administered to three patients. Case reports are summarized in table 1. The immediate results are summarized in table 2, while the course of each patient after treatment is outlined in table 3.

<sup>12</sup> Thorn, G. W., Forsham, P. H., Prunty, F. T. G. and Hills, A. G.: Test for adrenal cortical insufficiency: Response to pituitary adrenocorticotrophic hormone. *J.A.M.A.*, 137: 1005-1009, 1948

<sup>13</sup> Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Roche M., Stachelin D. and Wilson, D. L.: Clinical usefulness of ACTH and cortisone. *New Eng. J. Med.*, 242: 783-793; 824-834; 865-872, 1950.

Significant observations are:

a. In none of the patients has there been any marked cystoscopic change, save for slight diminution in the area of ulceration in cases 1 and 3.

b. Relief of dysuria is rapid in onset, but of variable and unpredictable duration.

c. Bladder capacity in all 3 cases has been doubled.

d. Despite complications of the disease such as hemorrhage and recurrent pyuria, in two of the 3 patients there was no prolonged recurrence of the severe dysuria or nocturia, and in each instance bladder capacity has remained at a reasonable level. Duration of initial beneficial effect has varied from less than one

TABLE 3. *Post ACTH course*

| CASE NO | DURATION OF INITIAL BENEFIT | COMPLICATIONS                                             | THERAPY OF COMPLICATIONS       | FOLLOW UP                                                                                                             |
|---------|-----------------------------|-----------------------------------------------------------|--------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| I       | 2 months                    | Recurrent pyuria without frequency, dysuria during attack | Chemotherapy                   | 9 month period with recurrent pyuria. Symptomatology markedly decreased between attacks. Nocturia increased gradually |
| II      | 2 weeks                     | Hematuria                                                 | Fulguration of bleeding points | 6 months without dysuria. Gradual return of nocturia. Dyspareunia decreased. 2 episodes of hematuria                  |
| III     | 4 days                      | Recurrent nocturia and dysuria                            | Nonspecific                    | Gradual subsidence of symptoms over 4 month period. Capacity 200 cc. 1 episode of hematuria 1 month after treatment   |

week to months, with gradual recurrence of symptoms of bladder irritability in two of the three patients.

#### DISCUSSION

It would appear from these initial observations that complete and permanent arrest of the process has not occurred. Nevertheless, we believe that definite benefit from the use of ACTH has been obtained, and that further observations and study are warranted, since it is too early to evaluate the ultimate result. It is possible that the most propitious time for the administration of the agent has not yet been ascertained, and that one should not await the appearance of symptoms or signs of vesical injury before utilizing the drug. Perhaps, the coincidental administration of the drug during radiation treatment or repeated courses of ACTH may be necessary to completely avoid the untoward sequelae. The use of ACTH in depoform on an ambulatory basis also remains to be explored.

It is apparent from this preliminary study that relief of discomfort can be ob-

tained. This in itself may render the therapy of value in patients who are markedly disturbed emotionally, or in those whose rest and convalescence from the therapy of their primary disease has been interrupted. The anesthetic effect of ACTH, as manifested in these cases by the relief of dysuria, has been observed previously,<sup>14</sup> and although its exact mechanism is unknown, it is a property shared with many steroids.

Furthermore, this study leads to the question of what effect ACTH will have on other forms of radiation sickness,<sup>15</sup> and whether or not the late effects of radiation therapy for genito-urinary disease per se can be avoided. To date, 2 patients in this category have been treated, and although it was impossible to obtain objective evidence of improvement in one of them, due to the advanced state of the patient's disease, it was believed, both by the patient and his attending physician, that benefit had been attained. The other had definite increase in bladder capacity, and concomitant relief of symptoms.

Finally, this early presentation is made with the hope that others will use ACTH in this type of disease and evaluate it in order to obtain a true perspective of the therapeutic efficacy in terms of common experience and significant numbers of cases.

#### SUMMARY

The use of ACTH in radiation cystitis has been discussed. Three cases have been presented and immediate beneficial effects described.

<sup>14</sup> Selye, H.: Anesthetic effects of steroid hormones. *Proc. Soc. Exper. Biol. & Med.*, **46**: 116-121, 1941.

<sup>15</sup> Taber, Kenneth W.: Treatment of radiation sickness with ACTH; preliminary report of 14 cases. *Radiology*, **57**: 702, 1951.

## DELAYED CYSTOGRAMS IN CHILDREN

RAYMOND G. BUNGE

*From the State University of Iowa College of Medicine, Iowa City, Iowa*

At Washington, D. C., in 1949, Dr. Charles M. Stewart of Los Angeles discussed a paper, "Abnormalities of Kidney, Ureters and Perinephric Fascia," by Benjamin and Tobin. During his comments he showed several slides of "delayed cystograms" that demonstrated ureteral reflux not ordinarily observed on the opaque cystogram. This paper reports our own observations with Stewart's technique.

### METHODS

In all children suspected of having urological disease, routine excretory urography is performed. If this examination fails to reveal any disease, i.e., tumor, congenital hydronephrosis, etc., delayed cystograms are made on the following day. The 24 hour lapse eliminates confusion between intravenous dye and dye arising from ureteral reflux. Skiodan (75 to 150 ml. of 10 per cent solution) is instilled in the bladder by catheter. No effort is made to overdistend the bladder. The amount used varies. A feeling of fullness is the principal clinical guide. The catheter is withdrawn and a roentgenographic exposure in the anteroposterior view is made immediately over the bladder and the kidneys. The patient is allowed ambulation and exposures are made thirty and sixty minutes after the instillation.

### OBSERVATIONS

Five normal children ranging in ages from three to eighteen years were examined by delayed cystograms and no ureteral reflux appeared. This supports past and current opinion that in the presence of normal ureterovesical physiology the phenomenon is absent.

Tabulation of observations is given in table 1.

By way of example, 2 cases have been selected for presentation:

M. M., a white girl aged 3 years, came to the clinic with a history of acute recurrent episodes of urinary tract infection. Birth and development had been normal and no congenital defects had been noted. The physical examination was essentially normal. The urine was acid, chemically negative and microscopically contained many white blood cells. Hemoglobin was 13 gm. per ml. and the white blood cell count was 12,400 per cu. mm. Residual urine was not found.

Excretory urograms showed bilateral hydronephrosis. Cystoscopy revealed a normal bladder and outlet. Delayed cystograms were made (fig. 2). The initial cystogram (fig. 2, A) demonstrates no visible ureteral reflux of skiodan. A cystogram made 30 minutes later with patient retaining original instillation (fig. 2 B) shows bilateral ureteral reflux. A cystogram made 60 minutes after instillation shows only left ureteral reflux (fig. 2, C). This case illustrates the interesting and unsuspected ureteral reflux, not detected by other techniques of examination.

P. B., a white girl aged 9 years, came to the clinic with a history of recurrent,

TABLE I

| PATIENT | AGE | SEX | CONDITION                                                                                | RESIDUAL | CYSTOSCOPY                                  | CYSTOGRAMS |             |             |
|---------|-----|-----|------------------------------------------------------------------------------------------|----------|---------------------------------------------|------------|-------------|-------------|
|         |     |     |                                                                                          |          |                                             | 0 min.     | 30 min.     | 60 min.     |
| M. M.   | 7   | F   | Recurring urinary tract infection                                                        | 100 ml.  | Cystitis                                    | No reflux  | Left reflux | Left reflux |
| G. T.   | 7   | F   | Polyps at bladder neck                                                                   | None     | Polyps                                      | None       | None        | None        |
| D. D.   | 6   | M   | Neurogenic bladder, secondary to poliomyelitis                                           | 100 ml.  | Dilated bladder neck, coarse trabeculations | None       | None        | None        |
| M. M.   | 3   | F   | Urinary tract infection                                                                  | None     | Normal                                      | None       | Bilateral   | Left        |
| P. B.   | 9   | F   | Recurring urinary tract infection                                                        | 10 ml.   | Trabeculation                               | Left       | Bilateral   | Left        |
| K. H.   | 6   | F   | Recurring urinary tract infection                                                        | 0 ml.    |                                             | Bilateral  | Bilateral   | Bilateral   |
| M. G.   | 8   | F   | Recurring urinary tract infection                                                        | 20 ml.   | Not done                                    | Bilateral  | None        | None        |
| L. L.   | 8   | F   | Meningomyelocele. Neurogenic bladder                                                     | 20 ml.   | Trabeculations                              | None       | None        | Right       |
| J. B.   | 15  | M   | Congenital bladder neck obstruction, congenital heart disease                            | 0 ml.    | Not done                                    | None       | None        | None        |
| W. S.   | 7   | M   | Postoperative congenital bladder neck obstruction, postoperative right ureterocystostomy | None     | Trabeculations                              | Left       | Left        | Left        |
| J. B.   | 5   | M   | Congenital prostatic valve                                                               | 5 ml.    | Trabeculation                               | None       | Bilateral   | None        |

acute episodes of urinary tract infection accompanied by left flank pain. Birth and development had been normal. No congenital defects had been observed. The physical examination was negative. Residual urine was 20 cc. The urine was



FIG. 1. *A*, initial cystogram with some lower left ureteral reflux. *B*, cystogram 30 minutes later with bilateral reflux. *C*, cystogram 60 minutes with only left ureteral reflux. (All refluxed.)

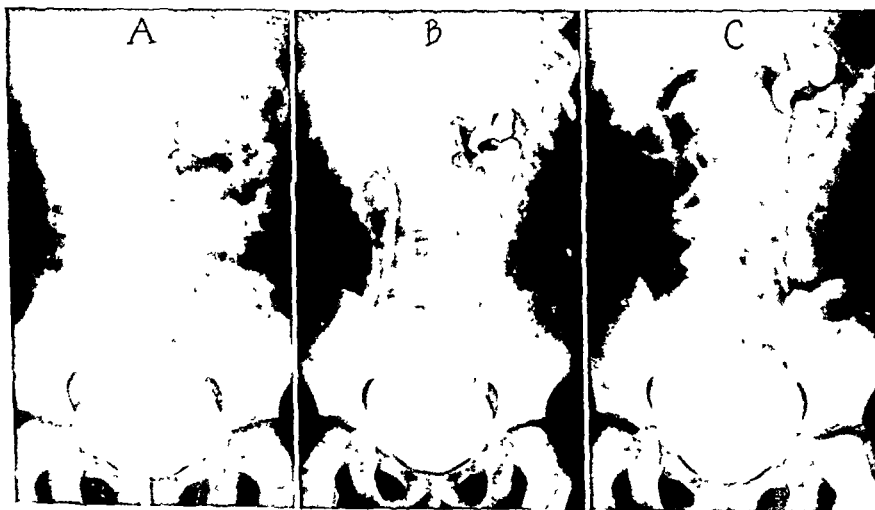


FIG. 2. *A*, initial cystogram, no reflux. *B*, cystogram 30 minutes showing bilateral ureteral reflux. *C*, cystogram 60 minutes, indicates only lower left ureteral reflux. (All refluxed.)

acid and was negative chemically and microscopically. Excretory urograms were normal. Delayed cystograms were made (fig. 1). The initial cystogram (fig. 1, *A*) shows a normal bladder with some reflux in the lower segment of the left ureter. A cystogram 30 minutes after instillation of skiodan shows bilateral ureteral re-

flux with pyelograms (fig. 1, *B*). A cystogram 60 minutes after instillation of skiodan shows again only the lower segment of the left ureter (fig. 1, *C*). Again, the technique has revealed an unsuspected clinically-significant abnormality in ureterovesical physiology.

#### COMMENTS

The use of delayed cystograms permits the radiographic observation of ureterovesical physiology, not at one instant of time, but at points along the time continuum. Unsuspected disease may be uncovered when other observations are normal, particularly when one is repeatedly baffled by normal findings in a child who has recurrent urinary tract infections. The damaging effect of ureteral reflux upon the kidney both by pressure and infection is well known. Consequences of failing to recognize it are grave both for the patient and clinician.

It is not the purpose of this paper to speculate upon the cause of this phenomenon, such as congenital defect, neurogenic dysfunction, chronic infection, etc., but to demonstrate the usefulness of a diagnostic procedure. Investigations are under way to elucidate the etiology and the possible correction of the reflux.

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BENJAMIN, J. A. AND TOBIN, C. E.: *J. Urol.*, **62**: 715, 1951.

## BENIGN MESOTHELIAL TUMORS OF THE URINARY BLADDER: REVIEW OF LITERATURE AND A REPORT OF A CASE OF LEIOMYOMA

EDWARD W. CAMPBELL AND G. JOHN GISLASON

The rare incidence of benign mesothelial tumors of the bladder and the infrequent presentation of this subject in the American literature during the past decade have prompted this review of the literature with a case report of a leiomyoma which afforded a diagnostic problem.

### CASE REPORT

A woman, aged 42, complaining of vesical distress and frequent urination, was referred for study in November 1944. Symptoms were of 1 week's duration having been recognized as lower abdominal distress followed by nocturia every 5 to 10 minutes. Diurnal voiding was required every  $1\frac{1}{2}$  to 2 hours. She had a constant sense of pressure in the region of the bladder with pain at the onset of urination. Further questioning elicited the tendency to more frequent urination of 2 years' duration.

The family history was irrelevant. In the past history one pregnancy in 1924, terminated by cesarian section, was noted. An appendectomy and right salpingo-oophorectomy had been performed in 1931. The patient had been under treatment for hypertension for 1 year, but the blood pressure was not elevated during our entire period of treatment.

General physical examination, including abdominal examination, was completely negative. Urinalysis was negative and the urine culture sterile. There was no residual urine.

The passage of a cystoscope was executed with ease. The bladder tolerance and capacity were normal. The mucous membrane pattern was normal throughout. At the outlet of the bladder a spheroidal intrusion was noted which elevated the floor of the bladder and pressed the left side of the vesical neck inward, also the urethra distal to this point. The urethra was carefully examined with a panendoscope searching for the orifice of a diverticulum but none was found. On vaginal examination a cystic mass was palpated in the region of the proximal urethra which extended anteriorly on the left side of the urethra and vesical neck. After removing the urethroscope, the mass was pressed and a thick gelatinous material was expressed through the urethra. This contained mucus, blood and pus. A diagnosis of a urethral diverticulum was made although the orifice had not been visualized.

Laboratory studies made after hospitalization revealed urinalysis negative, hemoglobin 11.9 gm., erythrocytes 3,360,000, leukocyte count 6,700. The blood Wassermann and Kahn tests were negative.

On November 15, 1944, under general anesthesia, the mass could not be pal-

Read at annual meeting Mid-Atlantic Section, American Urological Association, Philadelphia, Pa. April 17, 1952.



pated as distinctly as previously outlined. The urethra was exposed through a vaginal incision but no diverticulum could be identified. The incision was enlarged to expose the posterior bladder wall but no pathological changes were detected. Following this procedure, the patient voided freely and without distress, and was discharged on the fifth postoperative day.

Except for one attack of cystitis which was promptly relieved by chemotherapy, the patient remained comfortable until 1947 when she returned with nocturnal frequency, urgency and difficulty to void at night. During the day there was periodic frequency but no difficulty in voiding. She moved from Philadelphia and was referred to a urologist in another city but failed to visit him.

Later, in December 1948, she returned complaining of nocturia with urgency and difficulty to void. During the day more difficulty and straining were experienced and more frequency. Re-examination revealed a larger cystic mass at the region of the bladder base and excision of the mass was advised. On January 5, 1949, she was re-admitted to the hospital, at which time hematuria had appeared as a symptom for the first time during her long history.

Cystoscopy revealed a distorted urethral canal and a smooth intrusion of the left lower wall of the bladder due to a spherical mass. The mucous membrane overlying the mass was studded with small hemorrhagic areas which oozed blood. There was no ulceration or edema. The left ureteral orifice was displaced inward due to an intramural or extravescical pressure but was patent and the renal function was normal.

January 7, 1949, the bladder was mobilized through a suprapubic incision and a large, firm mass palpated within the wall of the bladder at its base on the left side. The bladder musculature overlying the growth was normal, and was not adherent to the surrounding tissue. The mucosal aspect of the growth revealed no changes suggesting a malignant growth. The bladder musculature overlying the mass was incised down to the growth which was found to have a firm, smooth, glistening surface. The growth was well encapsulated and was shelled from the bladder wall without disturbing the mucous membrane covering its surface. Frozen sections were immediately examined and the growth found to be benign. The cavity created by removal of the growth was obliterated and the bladder closed with urethral catheter drainage. The postoperative convalescence was uncomplicated and the patient was discharged January 25, 1949. Micturition was accomplished with ease and complete continence. The patient was last seen February 1952, three years following removal of the growth, at which time she was asymptomatic and no evidence of recurrence of the growth was evident.

Pathological report (Dr. Oscar Rambo): The gross specimen (fig. 1) consisted of a well circumscribed, rubbery and ovoid mass, 5.3 by 6 by 3.5 cm., almost completely covered with a thin, transparent capsule. On section the tumor was greyish pink in color and presented a whorloid area but was generally of a rather homogenous consistency. A few small, irregular areas of cystic mycoses were present averaging 1 to 3 mm. in diameter. These were presented as depressed, pitted areas on the cut surface.

Microscopic examination: The hematoxylin and eosin sections showed a fairly cellular leiomyoma with no significant mitotic activity. The cells were arranged in whorls and showed slight palisading. A Weigert-Van Geisen stain rules out the possibility of a neurofibroma. Diagnosis, leiomyoma (fig. 2).

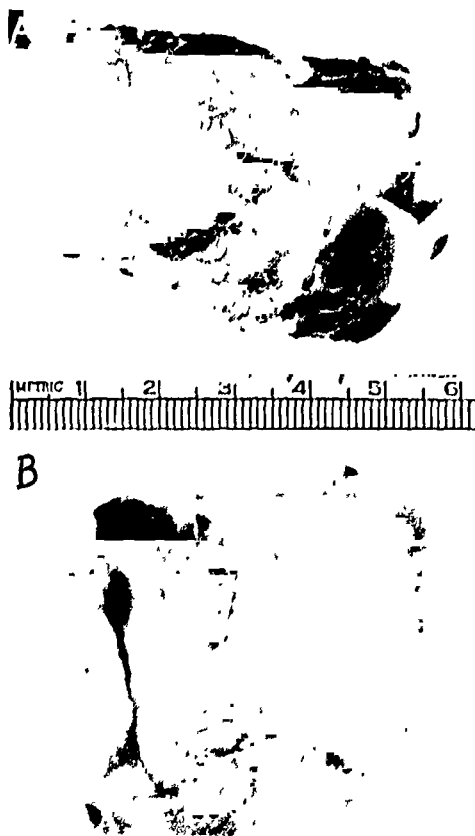


FIG. 1. *A*, shelled out tumor shows smooth outer surface covered by thin capsule. *B*, cross section of tumor reveals its homogeneous consistence and areas of pitting due to cystic degeneration.

#### CLASSIFICATION

Benign vesical tumors of mesothelial origin are subdivided into the following groups: 1) Myoma, a) fibromyoma, b) leiomyoma, c) rhabdomyoma; 2) fibroma, a) fibroma durum, b) fibroma molli; 3) angioma; 4) myxoma; 5) osteoma.

Osteoma has been added to the previous classification because of the report of such a tumor in 1911 by Collins and Welchier. These are said to arise from mesothelial elements as the result of metaplasia probably from reticulum cells (Herbut).

The recognition of mesothelial tumors as a class is more easily accomplished than allotment to the subdivisions according to the above classification. A review of the case reports in the literature indicates the frequent occurrence of mixed tumors which require a complex title to indicate their true cellular content.

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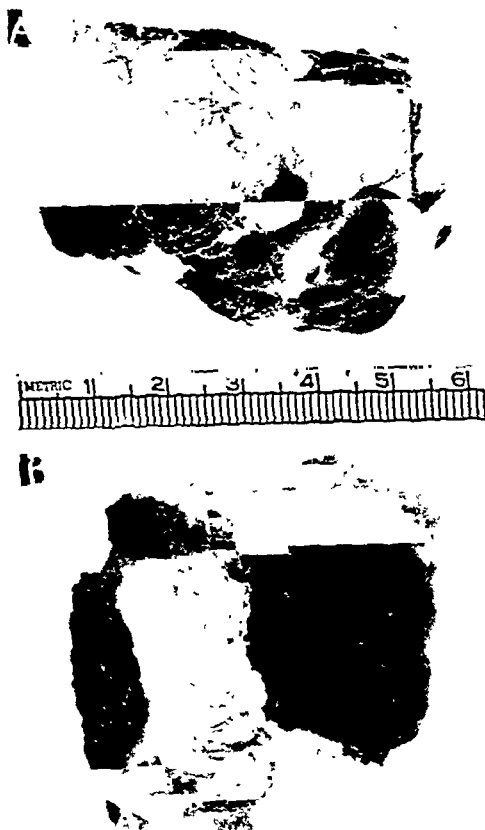


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The recognition of mesothelial tumors as a class is more easily accomplished than allotment to the subdivisions according to the above classification. A review of the case reports in the literature indicates the frequent occurrence of mixed tumors which require a complex title to indicate their true cellular content.

The name given to a tumor should naturally describe its cellular content as accurately as possible. However, the use of complex titles does not permit proper cataloging of these tumors if a simple classification is to be rigidly employed. A recent report of a leiomyomatous fibromyxoma by Sansone and Gillette defies allocation and must be relegated to a miscellaneous group of mixed mesothelial tumors. It would greatly facilitate identification of individual groups of tumors in this class if the predominant tissue were placed last when given a title.

The use of the term fibroids of the bladder could well be discarded for a more accurate description of a tumor when reporting a case. Pagel has recently

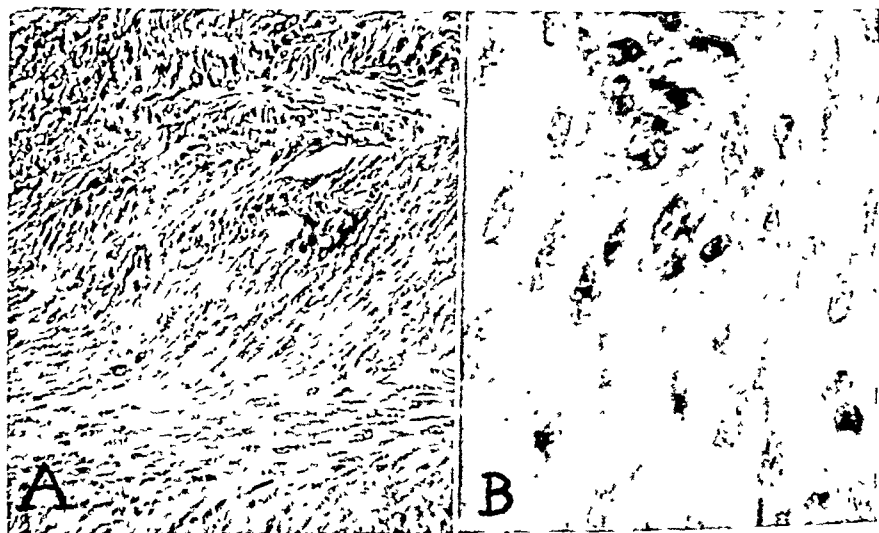


FIG 2 Photomicrographs. A, low power shows orderly arrangement of cells and evidence of palisading and no fibrous stroma B, high power shows smooth muscle fibers with regular, centrally placed nuclei which possess even staining qualities. Diagnosis. Leiomyoma.

stressed the necessity for careful differentiation of myomatous tumors arising at the vesical neck in the male from tumors of prostatic origin.

#### ETIOLOGY

Theories for the origin of these tumors are purely hypothetical and without scientific evidence for their validity. Claisse (quoted by Hertz-Boyer and Dore) suggested that perivascular inflammation caused by infectious agents on the walls of uterine vessels as the cause for uterine fibroids may be applied to vesical tumors. Blum (quoted by Kretschmer) suggested the development of myoma from hypertrophied bladder musculature, secondary to infection. Infection is infrequently reported and when found is undoubtedly secondary to the tumor so that the theory of infectious origin seems improbable.

Stone as a possible irritative factor has not been found in our review. Mcade reported a calcified myxomatous tumor in a child which simulated a calculus but it was his opinion the calcification was secondary to the tumor as a foreign body.

The simpler and more acceptable theories are those of embryologic origin. Sources of embryonic rests have been described as from a partially atrophied müllerian body (Verhoogen), from the urachus (Pilliet and Dupuy), supernumerary ureters (Riegel) and from a hydatid of Morgagni or the lower layer of the ureter (Hegal) (quoted from Koll). Although many mesothelial tumors occur frequently at the bladder base the fact that they are found in all parts of the bladder strengthens the theory of embryonic origin.

#### CLINICAL CHARACTERISTICS

It seems needless to lengthen this discussion with a description of the various cellular construction of these tumors for they are so well described in textbooks on pathology. There are, however, certain gross characteristics which are of clinical interest.

Mesothelial tumors show no predilection for sex, an equal number having been reported to occur in the male as in the female. Benign tumors have been reported to occur from the first to the eighth decade inclusive so that age is not a factor.

Myxomatous tumors occur more frequently in children. Surra has recently reported seventeen myxomatous tumors in children, all but one of whom were under 3 years of age. Deming (1924) reported 56.9 per cent of tumors in children in his review were malignant and Rathbun (1937) 56 per cent, suggesting that all tumors in children should be reviewed with suspicion of their benignancy. Fibrous and myomatous growths have been reported in children but usually occur after the second decade. Cawker, in a recent discussion of angiomas, stated that 50 per cent of the cases reported in the literature are under 20 years of age. Rathbun reported one in a child 27 months of age.

Myomas develop as submucosal, intramural or external growths. Submucosal tumors are usually pedunculated or polypoid. The base may be broad, as in Kretschmer's report, or narrow with a long, thin pedicle, which makes possible their protrusion through the urethral meatus in the female patient (Kutzmann and Cunard) or a ball valve type of obstruction in the male patient. Ulceration occurs which has caused hematuria to be a frequent symptom in reported cases. This type of growth has been removed locally by the transurethral or suprapubic route, and in some cases segmental resection has been used without recurrence of the growth regardless of the method employed.

Intramural myomas are surrounded completely by muscle of the bladder wall and are usually well encapsulated so that they may be shelled out with ease without destroying the surrounding tissues. This was possible in our patient and has been reported by others (Tettamanti) without recurrence of the tumor. Intramural tumors vary in size from small to quite large tumors but do not account for the large tumors reported. They frequently develop near the bladder base and cause symptoms of obstruction. Those occurring on the posterior wall or fundus are usually recognized by the symptom of hematuria or at autopsy.

Benign tumors reported to have been found outside the bladder and in the abdomen are usually fibrous or fibromyxomatous growths. These may grow to

enormous size; the largest reported by Kouzenetzki weighed 9 kilograms. The tumors are attached to the bladder by a small pedicle. Michon (1924) reported a double fibroma attached to each other by a narrow isthmus, one being attached to the bladder by a small pedicle. Recently Kleitsch has reported a fibromyoma weighing 3395 gm. with a vicarious vascular supply which again was attached to the bladder by a delicate pedicle.

Fibromas usually develop from the submucosal connective tissue, are covered with mucous membrane and are recognized as pedunculated or polypoid growths. Intravesical growths have not attained great size and can be resected transurethraally without fear of recurrence.

Angiomas have been reported more frequently in recent literature. They are described as occurring most frequently in the dome of the bladder and are usually associated with similar lesions in other organs. Abeshouse has reported finding one in a diverticulum. The outstanding symptom has been hematuria. Cure has been reported with transurethral fulguration. This is a dangerous procedure for the vessels may penetrate the muscle wall and severe hemorrhage ensue. Hemangioma must be distinguished from vesical varices.

#### FREQUENCY

The rare occurrence of benign mesothelial tumors can be supported by various methods of reasoning. We have been able to find only 38 references in the literature to this disease since 1936. Each reference deals with the report of a single case with the notable exception of Samenius (1949) and Castano (1945), each of whom reported 2 cases. Prior to this time Judd had reported 2 fibromas in 164 vesical tumors and Motz, 3 myomas in 87 vesical tumors. It would seem from this that only one or two benign mesothelial tumors at the most are found by any one urologist during his period of practice.

Beer who reported 600 vesical tumors stated that benign tumors might be an incidental finding but did not include them in his series. Nitze (quoted by Kretschmer) failed to report this type of growth in 39 vesical tumors as did Young, 380 cases; Scott and McKay, 622 cases; and MacKenzie, 500 cases.

In the latest study of the carcinoma registry (April 1950), Dean and Ash reported 5324 bladder tumors. Leiomyoma is mentioned in the classification under miscellaneous tumors but the number not specified; it could be either one but not more than two. It is usually stated that benign tumors account for 10 per cent of all vesical tumors. Kutzmann found 1 leiomyoma among 202 bladder tumors (0.49 per cent). In a survey of vesical tumors which we are now making of 500 cases, we have encountered the one tumor we are presenting in this paper. This would suggest an incidence of benign mesothelial tumors of the bladder rarer than previously suspected.

#### REVIEW OF LITERATURE

The literature has been reviewed in order to determine the number of each type of benign mesothelial tumors reported since the last authoritative review

in the American literature and to bring the bibliography up to date for future reference. Each type will be discussed in this respect under separate heading, according to the classification.

*Fibromyoma.* Koll's review in 1923 has been used as a base line for most American writers. He collected 38 cases of "fibroids of the urinary bladder," twenty-eight of which were grouped as 16 myomas, 1 myofibroma, 8 fibromyomas, 2 leiomyomas and 1 myxofibroma. The myomas appear to have been simple tumors of striated muscle, as described by Heitz-Boyer and Dore in 1910. These cannot be included under the subhead of fibromyoma. The two myofibromas can be placed in this category, making a total of 10 cases.

White reported a case in 1931 and later Geisinger (1933) added another bringing the total to 12 cases. Since this report we have been able to find 10 additional reports (Castano, Cahy, Canard, Iacapraro, Kleitsch, Oliva, Perard, Reist, Scrufari and Tettamanti), thus bringing the total number of fibromyoma to 22 reported cases.

*Leiomyoma.* De Barne-Lagarde (1929) carefully reviewed the literature and collected 36 authentic cases of leiomyoma. Using this as a basis, Kretschmer (1931) found 11 case reports in the literature and added one of his own. Kretschmer included an angiomyoma reported by Kidd and Turnbull because the tumor contained smooth muscle fibers. This was not a pure leiomyoma but a mixed tumor and should not be included. Therefore, instead of there being 48 cases as he reported, there were 47. Geisinger (1933) added 2 cases, one of his own and one reported by White in 1931. Both tumors were fibromyoma and, instead of bringing the total to 50 as he indicated, there were only 47. Keene and Thompson (1935) reported 1 case and collected 9 from the literature. These, including Geisinger's case, made a total of 59 cases. These authors used Kretschmer's review as a base line and added 5 cases which were overlooked by him (Latyka, 923, Smith, 1928, Segurola, 1928, 2 cases, Maingot, 1929). They included four case reports which appeared in 1931, one of which was reported by Higgins as a fibromyxoma. Another was White's case, a fibromyoma previously added by Geisinger. There were, therefore, only 8 additional cases, theirs included, thus making the total fifty-five. Kutzmann (1937) and Grauer (1938) added one case respectively, bringing the total to 57. This number does not comply with the records of either author's review because of the discrepancies mentioned above. Since 1938 we have been able to find 10 additional case reports (Castano, Cibert, Gouverneur, Monserrat, Magase, Pagel, Sameniums, Samuel, Sersal and Serra). These, with the case we are reporting, should bring the number of reported cases of leiomyoma to 68.

*Rhabdomyoma.* Except for osteoma this is the rarest of all mesothelial tumors. Ewing referred to 4 reports in the 1940 edition of *Neoplastic Diseases* (Cattani, Vincenzi, Stumpf and Mönckeberg). Deming (1924) in a survey of 64 bladder tumors in children reported one from the literature and added his case. Rathbun (1937) in a similar survey recorded the cases presented by Deming. Khoury and Speer (1944) in a review of rhabdomyomatous tumors recorded 9 cases from



the literature, six of which had not been recorded by the previous authors (Paronne, Huesler, Shattock, 4 cases). Since these reviews we have found an additional case report by Dierickx which would bring the total to 12 cases.

*Fibroma.* Koll, in 1923, collected 3 reports of pure fibroma and added 1 case. Martin, in 1936, reviewed the literature and found 10 additional cases to which he added 1 case, bringing the total to fifteen. He, however, included Geisinger's case which tumor contained smooth muscle fibers and was not a pure fibroma. Thus the total was 14 cases. In the same year Pearson reported an additional case which brought the total to 15 cases in 1936. Since then we have found only one additional case report (Noe 1943). This brings the total to 16 reported cases of fibroma.

*Angioma.* Kahle, Maltry and Vickery reviewed the literature and added an additional case in 1942, bringing the total to 41 cases. It is interesting that Segal and Fink in the same year published a case report and review and found the same number of cases. Therefore, in 1942, there had been 42 cases reported. Riches, in 1951, suggested the possibility of 43 cases reported to that time. We have found a case report by Manenti, published in 1940, which was not mentioned by the above authors. We have been able to find 9 additional case reports (Abeshouse, Bernandi, Cawker, Kahle, Kny, Manenti, de la Peña, Riches and Segal). This would bring the total number of reported cases to 51.

*Myxoma.* Rathbun (1937) collected 75 tumors in children, sixteen of which were myxomas. We have been able to find only 3 cases reported since that time, two of which were mixed tumors; Bongiorno, fibromyxoma; and Sansone, a leiomyomatous myxofibroma. The addition of these cases to this group is controversial so that the total number of myxomas may be considered as seventeen with the addition of two mixed tumors of myxomatous character. Because of this trait, we are including them in this group to make a total of 19 benign myxomatous tumors.

#### SUMMARY

A careful review of the literature was made to ascertain the incidence of benign mesothelial tumors. The reports of 192 cases have been found to which we have added another case to make a total of 193 cases.

Using a recognized classification we have separated these tumors into the various groups designated in this classification. The distribution resulting from this breakdown has shown the following:

1. Myoma
  - A. Fibromyoma, 22 cases
  - B. Leiomyoma, 68 cases
  - C. Rhabdomyoma, 16 cases
2. Fibroma, 16 cases
3. Angioma, 51 cases
4. Myxoma, 19 cases
5. Osteoma, 1 case

## CONCLUSION

A case of leiomyoma of the urinary bladder has been presented which afforded some difficulty of diagnosis because of our lack of alertness to the possibility of this type of intramural growth.

The rarity of these tumors has been discussed and statistical evidence of this fact presented.

The classification has been amplified to include osteoma, a case of which has been reported recently.

The literature has been reviewed to include the reports of all types of benign mesothelial tumors of the urinary bladder to the present time.

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## CASE OF EPISPADIAS WITH A DOUBLE URETHRA

EDGAR A. SLOTKIN AND ALVIN MERCER

*From the Department of Urology, University of Buffalo Medical School, and  
Buffalo Children's Hospital, Buffalo, N. Y.*

A rare congenital anomaly is reduplication of the male urethra. De Berne-Lagarde stated that only 38 cases had been reported to 1932. Since then scattered case reports have appeared in the literature.

Chauvin has divided these cases into five types: 1) complete reduplication from glans to bladder (rarest type); 2) incomplete reduplication; accessory urethra ends blindly proximally and lies ventral to true urethra; 3) incomplete reduplication; accessory urethra ends blindly proximally and lies dorsal to true urethra; 4) Y-urethra with accessory urethra ending in true urethra distal to external or internal sphincter; 5) Y-urethra with accessory urethra opening at penoscrotal junction and joining normal urethra somewhere proximal to this.

Many theories have been advanced to explain the etiology of the congenital malformation. However, the most generally accepted one is that the anomaly is due to a continuation of the splitting process of the urorectal septum with a consequent bifurcation of the urethral anlage into a dorsal and ventral portion, partial or complete.

The symptoms vary with the types: type 1, incontinence, since the opening is above both sphincters; type 2, asymptomatic unless urethritis develops; this may be the presenting problem, a stubborn, recurring discharge which will persist unless the accessory urethra is treated; types 4 and 5, a double stream during urination, with incontinence, if the junction is proximal to the external sphincter.

Usually no operative treatment is necessary unless there is persistent infection or incontinence. If so, either obliteration of the lumen with high frequency current or excision of the accessory urethra may be performed.

### CASE REPORT

J. M., an 8 year old white boy, was admitted to Buffalo Children's Hospital September 13, 1949. His mother had noted two openings on his penis which had been present since birth and that he urinated through both. The patient could hold his urine satisfactorily, but when he voided there was a spray from the epispadic opening and he wet himself intermittently due to lack of control in the accessory channel under stress. He had had intermittent attacks of frequency and dysuria during his childhood but these were never severe enough to necessitate medical care. The child had been a normal full term delivery, except for the congenital defect mentioned.

Examination disclosed a well developed but thin boy. Temperature 100F (rectal), pulse 100/min., respirations 22/min.

The scrotum was normal. The testicles were normal in size, shape, consistency and position. An open groove lined with mucosa extended from the glans along the dorsal surface the length of the shaft of the penis and dipped deep to join the

Accepted for publication November 25, 1952.

posterior urethra. There was also a normal urethral opening with a dorsal chor-dee (fig. 1).

On voiding, a good stream was passed through the normal urethra, with a spray from the dorsal groove. An incontinent spray was also noted from the accessory channel under conditions of stress or excitement. There was no evi-

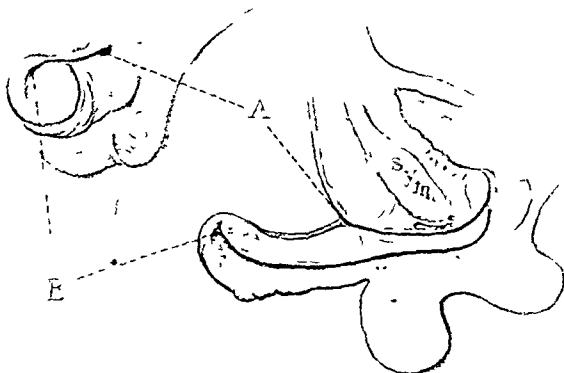


FIG. 1. *A*, epispadic opening. *B*, normal urethra

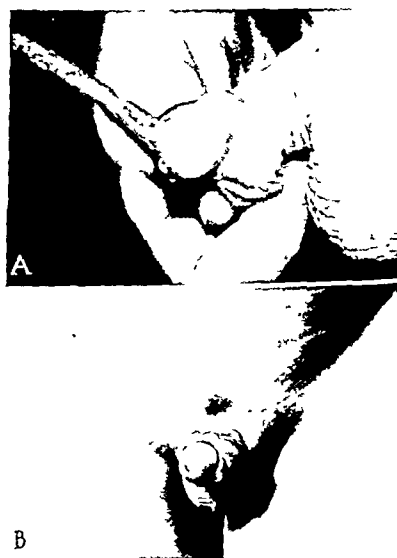


FIG. 2. *A*, dorsal chordee showing direction of urinary stream before correction *B*, end result. No chordee present; stream normal in size and direction.

dence of inflammation or discharge on examination. Rectal examination disclosed that the sphincter tone was good; the prostate was small and felt normal.

Laboratory findings: Urinalysis, pH 5.5; albumin, sugar and microscopic were negative. Hemoglobin, 14 gm. White blood cells, 14,900. Blood urea nitrogen, 96 mg. per cent. Serology, negative.

An excretory urogram made on September 16, 1949 showed good kidney function and normal outlines of kidneys and ureters.

On September 29, 1949, a urethrogram was made. The normal urethra was easily demonstrated, but despite several attempts to do so, no satisfactory outline of the accessory (epispadic) urethra could be obtained. However, when a small catheter was passed through the accessory channel, urine was obtained. In view of this and the intermittent stress incontinence, it was believed that the accessory channel opened in the posterior urethra.

On September 22, 1949, the accessory urethra was undermined and excised and the posterior aspect of it was buttonholed so that it opened downward toward the posterior urethra. The patient was returned to the ward in good condition with an indwelling catheter in place.

Postoperatively, 300,000 units of penicillin were given daily and the patient made an uneventful recovery. The catheter was removed on the twentieth postoperative day, and a urethrogram the next day showed the urethra to be well visualized, radiographically appearing normal. The patient was discharged on the twenty-seventh postoperative day, at which time he could void without difficulty and had no leakage or drainage from the previous epispadic opening.

Pathology report: Simple fibropapillary and papillomatous hyperplasia surface epithelium; no anaplastic features.

The patient was re-admitted August 31, 1950 with a diagnosis of acute appendicitis for which an appendectomy was performed. Recovery was uneventful.

Following this, a repair of the dorsal chordee previously noted was performed September 13, 1950. The scar tissue on the dorsal surface of the penis had increased the chordee so that the patient had to hold the penis downward or he would wet himself (fig. 2, A). This was dissected free and the skin on the ventral surface buttonholed and brought to the dorsum of penis, thus forming a prepuce. At the end of surgery, the penis was much longer and straighter than before.

The indwelling 16F Foley catheter was removed on the fourth postoperative day. However, on the sixth postoperative day, some urine started to leak through the suture line on dorsum of penis. This gradually decreased in amount until no drainage was observed on the fourteenth postoperative day. A urethrogram made on the twenty-first postoperative day was reported normal. The patient was discharged on the twenty-third postoperative day, the incision being healthy and voiding normally.

Pathology report: Chronic inflammatory reaction deep to surface epithelium of the prepuce; no specific process.

The patient was last seen January 11, 1952. There was no evidence of chordee and the incision was healthy (fig. 2, B). He was able to void normally without difficulty and has had no urinary distress of any kind since last admission. Whereas before surgery his clothes were always wet, he now has complete urinary control and is socially acceptable.

#### SUMMARY

An unusual case of reduplication of the male urethra with the accessory channel being epispadic is presented. No other case exactly like the one just described has been found in the literature. Excision of the accessory channel and repair of the dorsal chordee produced a satisfactory result.



## DOUBLE URETHRA: CASE REPORT

CAPT. MALCOLM W. ARNOLD (MC, USN) AND  
LT. WILLIAM M. KAYLOR (MC, USNR)

*From the Urology Service, U. S. Naval Hospital, Great Lakes, Ill.*

The congenital anomaly of double urethra is extremely rare and refers only to those cases in which there is complete duplication of the entire urethra in a single penis. The two channels emerge independently from the urinary bladder and extend distally in parallel fashion and without intercommunication. Double urethra should be differentiated from the more common anomaly of accessory urethra, which consists of duplication of only a segment of the urethra. Taruff's classification of the various types of accessory urethra is briefly outlined by Irmisch and Cook.<sup>1</sup> The most common variety of accessory urethra opens on the dorsum of the penis, runs inward for a distance of one to several centimeters and ends blindly without any connection to the urinary tract.

Gross and Moore<sup>2</sup> have summarized in table form the available information regarding cases of double urethra. Including one of their own, they analyzed a total of 19 cases. They pointed out that only in 7 instances was urinary incontinence the predominant symptom. Surgical excision was carried out in only 5 cases, all of which belonged to the incontinent group. In 5 patients they reported a continent but disturbing double urinary stream, and in 3 cases, gonorrheal infection. Two of the patients were troubled by an abnormally dorsal position of the penis either in the flaccid or erectile states. This dorsal angulation was thought to be due to the bow-string action of the dorsally situated urethra because of its attachment to the bladder or to the undersurface of the pubes. In the case report to follow, the patient's chief complaint was that of dorsal curvature of the penis, so excessive as to preclude any possibility of natural sexual intercourse.

### CASE REPORT

R. R. E. (Hospital Register No. 220091), a 20 year old white man, was admitted to this hospital in February 1952, for the treatment of primary atypical pneumonia. Pertinent urological findings included an epispadias-like groove, 1 centimeter in length, located at the mid-dorsal aspect of the glans penis. This groove extended to a small external opening situated at the balanopreputial groove (fig. 1, A). A second, larger opening appeared entirely normal except that it was displaced several millimeters dorsal to the usual position of the external urethral meatus. In the flaccid condition the penis exhibited a slight dorsal curvature. In the erect state, however, extreme curvature was apparent (fig. 1, B), and readily explained the patient's inability to have sexual intercourse. By

The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval service at large.

Accepted for publication November 4, 1952.

<sup>1</sup> Irmisch, G. W. and Cook, E. N.: *Minn. Med.* 29: 999-1002, 1946.

<sup>2</sup> Gross, R. E. and Moore, T. C.: *Arch. Surg.*, 60: 749-761, 1950.

palpation of the erect penis the dorsal urethra seemed to be the factor responsible for the marked angulation.

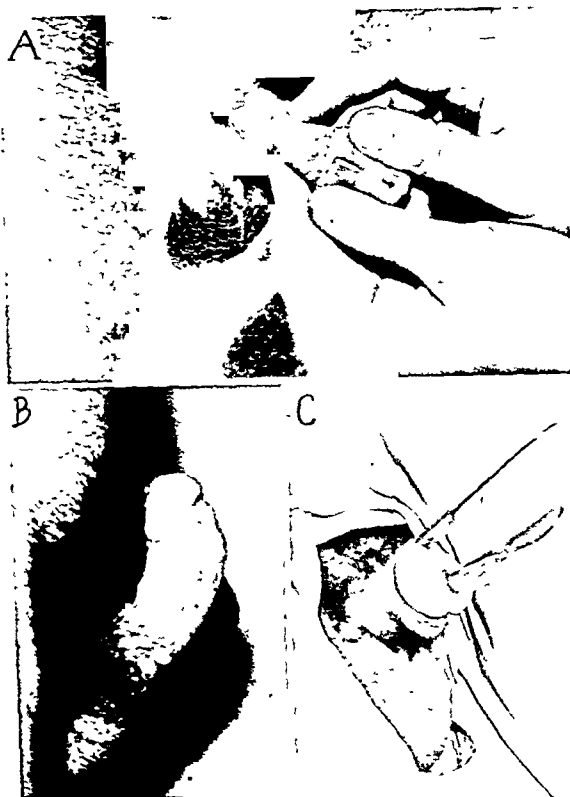


FIG 1. A, dorsal view of penis showing external orifices of double urethras. B, showing extreme dorsal angulation of erect penis; patient in standing position. C, 20F metal sound in dorsal urethra and a 24F sound in ventral urethra.

The patient had no complaints with regard to the act of micturition. Although urine could be passed simultaneously from both urethras, the patient could easily occlude the dorsal outflow by gentle digital pressure just proximal to the dorsal opening. He was completely continent of urine. During ejaculation semen passed only from the ventral urethra.

Examinations of the blood and urine were normal. Excretory urograms showed no abnormalities of the upper urinary tract.

Several methods were used to establish the diagnosis of double urethra. Catheters were simultaneously passed through both urethras into the bladder, and urine flowed freely through each catheter. A 24F metal sound was readily passed to the urinary bladder by way of the ventral urethra, and at the same time a 20F metal sound was passed along the dorsal urethra into the bladder. With both sounds in position (fig. 1, C) it was possible to obtain a metallic click. Endoscopic examination of the ventral urethra revealed a normal appearing verumontanum and no evidence of intercommunication of the two urethras.

The urinary bladder appeared normal except for the anomalous urethral orifices which, on retrograde visualization, appeared as two separate midline openings, one above the other, completely divided by a thin, membranous, transverse, tissue septum. A 6F ureteral catheter, introduced through the external opening of the dorsal urethra, was readily passed into the bladder where it was seen to enter through the more anterior urethral orifice. A voiding cysto-urethrogram clearly demonstrated the parallel course of the two channels from the bladder distally to their respective external openings. The course of the ventral urethra from the bladder was entirely normal. The two urethras were in close approximation near the bladder neck, and it was thought that they had a common external sphincteric mechanism.

The treatment in this case necessarily involved a surgical procedure designed to correct the severe degree of dorsal curvature of the penis without damaging the external sphincter. It was further believed that such a procedure should be based upon assumption that the dorsal curvature was due to the taut, bow-string action of the fixed dorsal urethra. We considered that total excision of the offending dorsal urethra, as described by Gross and Moore, would have been the procedure of choice had it not been for the fear of damaging the external sphincter and of rendering the patient incontinent. A more simple and innocuous procedure was therefore adopted whereby it was expected the curvature could be relieved, first, by lifting the dorsal urethra from its superficial bed along the entire penile shaft, and then, following ventral over-correction of the dorsal curvature, by replacing the dorsal urethra in such a relaxed position that its distal opening would be anchored without tension at about the mid-shaft position. In actuality, this was only a part of the anatomical problem in that many dense fibrous bands were found to be contributory to the dorsal curvature. Following a complete dissection of these bands which merged indistinguishably with Buck's fascia the penis appeared to be straightened. The patient made an uneventful recovery from the operation except that the approximated flaps of Colles' fascia and of the skin distal to the newly situated opening of the dorsal urethra separated and subsequently healed by secondary intention. The dense scar that eventually resulted caused a recurrence of the dorsal curvature to such a degree that no permanent benefit could be attributed to the operation.

#### SUMMARY

Cases of double urethra are extremely rare. By definition they are to be differentiated from the more common accessory urethras. A collective review of 19 cases of double urethra is referred to and our own case is presented.

## OCCURRENCE OF BONE TISSUE IN THE HUMAN PENIS

J. A. EGLITIS

*Department of Anatomy, The Ohio State University, Columbus, Ohio, and the  
University of Latvia*

Furuta (1924) states that: "Formation of bone tissue in the human penis, usually called os penis, belongs to the category of very rare phenomena." Thus the following observations may be of interest.

We received the cadaver of a 28-year-old executed convict, 4 hours post mortem, for histological purposes. Various organs were used to make histological preparations. No visible pathological changes were observed in any of them. The penis was also amputated for the same purpose. Nothing conspicuous could be seen in a macroscopic way. The penis was comparatively long, of a considerable circumference and had a normal appearance. The corpus penis was fixed in formol-alcohol, embedded in celloidin, cut in sections of 20  $\mu$ , and stained with hematoxylin and eosin and according to the method of Van-Gieson.

Cutting the preparation reminded one of the familiar sound heard when undecalcified bone is present. Microscopical examination showed an almost circular layer of small bony trabeculae in the subcutaneous connective tissue in the area of the fascia (fig. 1)

Many bone plates were seen particularly in the dorsal and lateral parts of the penis, fewer in the region of the urethra. The trabeculae were separated by loose connective tissue and had a construction typical of bone tissue: a homogeneous, partly lamellar intercellular substance with lacunae, where well preserved bone cells, osteocytes, were present (fig. 2).

The form and orientation of the bone plates were variable (fig. 3). Some were located near the epidermis, others closer to the corpora cavernosa; none, however, reached the tunica albuginea. The bone pieces were 5-8 mm. long and 0.5-2 mm. wide; thus the larger ones were visible macroscopically.

The edges of the bones were partly smooth, partly notched. It was significant that in some places there seemed to be a direct transition from fibrous connective tissue to bone tissue, as can be seen clearly in figure 4.

When stained with hematoxylin and eosin, the bone matrix had acquired an even reddish color, but the calcium depositions (which were scattered here and there at the edges of the bones and in the connective tissue close by, in the shape of granular strips and heaps) had acquired a violet-blue one (fig. 5).

In these sections the depositions of calcium salts and the genuine bone tissue could be distinguished so well because the preparation was not decalcified.

No typical bone-forming cells—osteoblasts—were observed. Except for the bone and precipitations of calcium no other peculiarities were disclosed in the penis. In fixed condition the diameter of the penis amounted to 28 mm. The cavernae were partly filled with blood, the blood vessels were of normal construction, the epithelium of the urethra was well preserved. No sign of inflam-

Accepted for publication July 30, 1952.

mation was located, only the largest pieces of bones were surrounded with comparatively many erythrocytes, which possibly pointed to some smaller effusions of blood.

Examining the sections, it was evident that the connective tissue was directly transformed into the bone tissue. Whether such a bony cover existed in the full

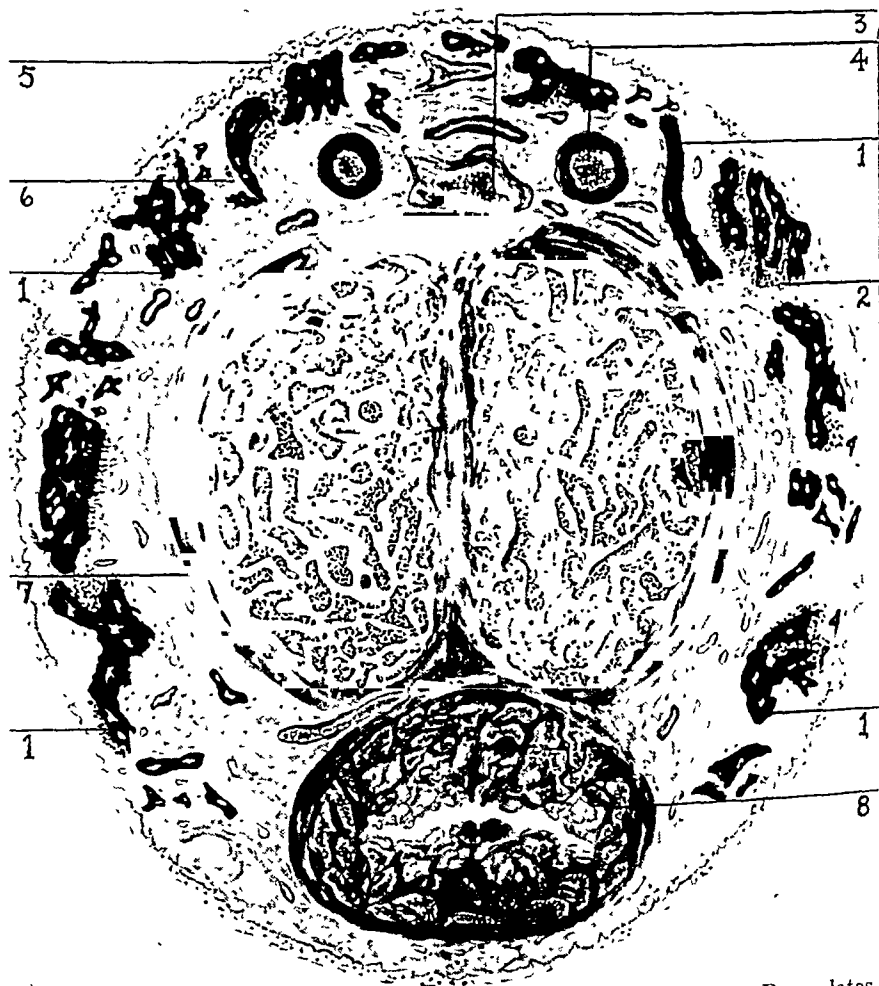


FIG. 1. Transverse section of corpus penis (semi-schematic drawing). 1, Bone plates. 2, Small effusion of blood 3, V. dorsalis penis. 4, A. dorsalis penis 5, Epidermis. 6, Area of fascia 7, Corpus cavernosum penis. 8, Corpus cavernosum urethrae.

length of the penis, we could not judge because only a part of the corpus penis was embedded. More than 500 serial sections were made from the corpus penis and all of them closely resembled the picture shown in figure 1.

It is known from the literature that several kinds of mammals (carnivora, rodentia, insectivora, cetacea) have in their penis a larger or smaller bone or cartilage, located in the septum or in the glans penis. They are called os penis, os glandis, also cartilago penis or os priapi. So, for example, big dogs have in

their penis an os penis of approximately 10 cm., located under the corpora cavernosa penis. The lower surface of the bone has a groove in which lodges the urethra. Also cats, particularly the older ones, almost always have on the tip of their penis a small, sharp os glandis, 3-4 mm. long provided with barbed hooks.

While the information about the os priapi of the animals is sufficient, the reports about the os penis of the nearest ancestors of men—the Primates and



FIG. 2 Bone plate in corpus penis in area of fascia.

especially the Anthropoidiae—are inadequate, indicating no systematic anatomical and histological investigation.

Arndt (1890) and Jacoby (1924) report that they have discovered in the penis of apes a bone a few mm. long. Furuta (1924) has examined the organs of copulation of 3 male chimpanzees and in all three of the penises an os glandis was located at the tip of the glans penis, in the connective tissue of the corpora cavernosa, dorsal to the urethra. Young animals had bones 5 mm. long and 0.75 mm. wide, adults—11 mm. long and 2 mm. wide. The bones were stick-shaped, compact with Haversian systems and a centrally located bone marrow cavity. The outer surface of the bone of a young animal was uneven and periosteal

growth was observed there. Moreover, no appositional growth of the bone could be traced in examining adult animals. This publication about the os penis of the apes by Furuta (1924) is the most comprehensive available in the literature.

The finding of so called "os penis" in the human organ of copulation has caused many discussions as to its origin, and as to comparison of it with the os penis of animals as well. These cases being very rare, the process of ossification has not been investigated sufficiently. At present we were able to find in the literature the descriptions of 25 cases only. The majority of these publications were based on clinical and roentgenological observations. Histological examination had taken place in only seven cases. Therefore, already Posner (1899) and

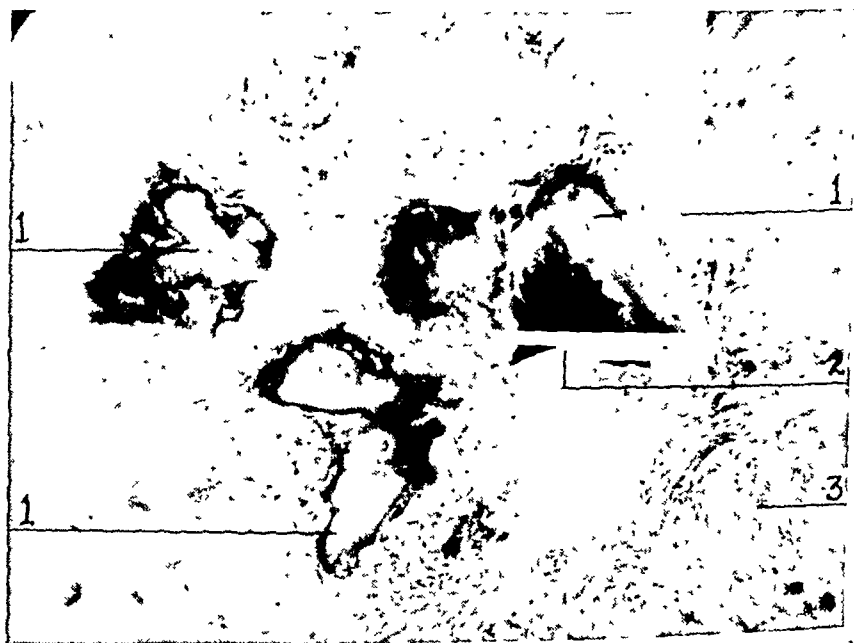


FIG 3 More frequent shape of bone plates in connective tissue of penis. 1, Bone plate 2, Deposition of calcium salts. 3, Connective tissue

later Furuta (1924) cautioned against considering every tangible callosity of the penis, even when visible in a roentgenogram, to be a bone. "It could possibly be an induratio penis plastica."

So, for example, the publications by MacClellan (1827), Malgaigne (1864), Merle (1899) and Kaufmann (1922) are based on clinical facts only. Siegmund (1874) tells about bone-like and cartilage-like structures, relying upon palpation. Foerster (1865) reports bone-like fibrous thickenings. Brohl (1904) and Navarro (1947) base this diagnosis upon the roentgenogram; Posner (1899) identifies cartilage or calcified connective tissue in the same way. The publications of Rokitansky (1863), Lenhossek (1874), and Koch (1907) are supported by gross anatomical examinations only, and all they have disclosed are pieces of bone or cartilage, whereas Robineau (1897) describes only calcifications.

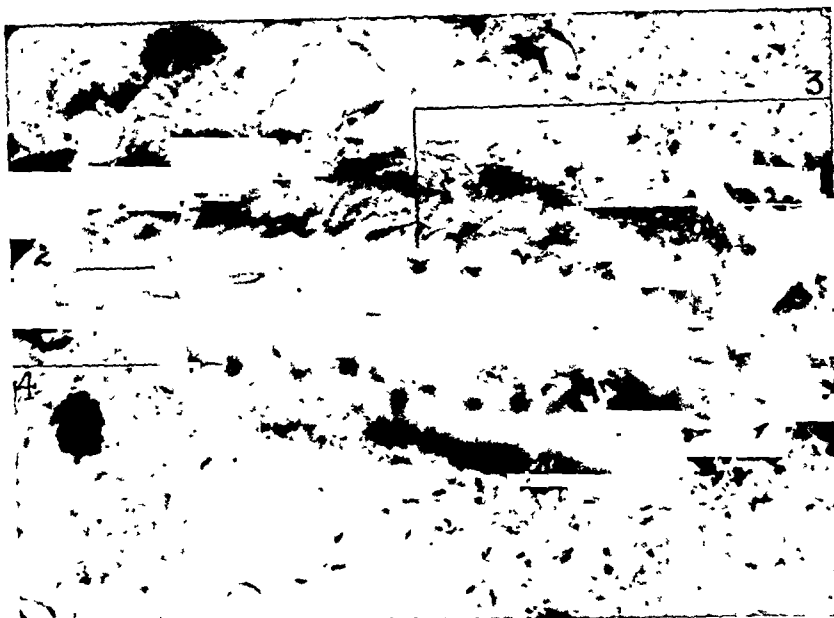


FIG. 4. Bone plate in connective tissue of penis. 1, Fibrous connective tissue. 2, Bone matrix. 3, Zone of growth. 4, Osteocyte.

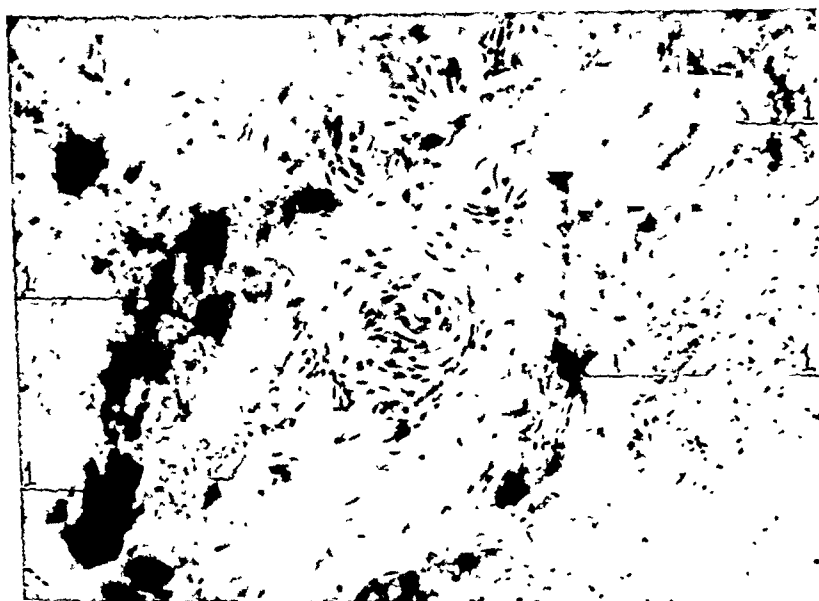


FIG. 5. Depositions of calcium salts in connective tissue of penis 1, Depositions of calcium salts

In cases up to now, discussed in the literature, os penis or cartilage has been observed in men of the age of 41-74; in the majority of cases the age was over 50, and only in one case was bony tissue discovered in a young man.



The localizations of the bone tissue in the penis are of different kinds. Hecker (1844), Lenhossek (1874), Siegmund (1874), Brohl (1904), and Kaufmann (1922) have observed bone tissue at the proximal end of the penis; whereas MacClellan (1827), Chetwood (1899), and Frangenheim (1907) have reported the presence of osseous tissue, the full length of the penis. Merle (1899) describes a bone cover surrounding the whole penis. In the majority bone tissue was found in corpus penis or in the dorsal part of the radix penis according to Furuta (1924) and other authors. The same conclusion resulted from our own work. The bone tissue was located in the region of the tunica albuginea or in the area of the fascia penis in the cases published by Hecker (1844), Rokitansky (1863), Malgaigne (1864), Foerster (1865), Siegmund (1874), Robineau (1897), Frangenheim (1907), Koch (1907), Furuta (1924), and Navarro (1947). In some cases the location was in the septum penis, according to the publications of MacClellan (1827), Malgaigne (1864), Foerster (1865), Lenhossek (1874), and Claude (1894), or even in the corpora cavernosa penis (Rey (1874), Siegmund (1874), Kaufmann (1922)). Mayer (1834) states that he found a small prismatic piece of bone in the center of the glans in the penis of vigorous men. The bone was developed more strongly in the penis of Negroes than in those of white people. Almost 100 years later another report of finding of bone and cartilage in the human glans penis was published (Vermooten, 1933).

Further, from a summary of the existing observations the size of the disclosed bones has been very variable. In the majority of the cases there have been thin bone plates 50 mm. long and 5 mm. wide. The number of them has been also different. For example, Robineau (1897) has found 5 ossa penis; Lenhossek (1874), 4; Furuta (1924), 2. On the contrary, in our case, the number of bone plates were considerably larger. The outer shape of the pieces of bone is of very different kind, too. There is not any similarity in this respect.

As already mentioned, very few authors have achieved histological examinations. These are Hecker (1844), Rey (1874), Claude (1894), Chetwood (1899), Frangenheim (1907), Furuta (1924) and Vermooten (1933). Hecker (1844) had at his disposal only one piece of bone extirpated from the penis of a living man. Thus it was impossible for him to relate any details concerning the relationships of the bone to the wrapping tissue. The piece of bone had "cartilagenous" edges and here and there some hollows, filled with "cartilagenous" substance.

Rey (1874) found osteoblasts on the surface of the bone, wherefore his conclusion has been that the bone was in a stage of growth.

Claude (1894), evidently, found no bone tissue at all, for he tells of a fibrocartilage calling it "enchondrom des corpus cavernosum penis."

Also Chetwood (1899) found only fibrous hardenings with the depositions of calcium salts in the connective tissue of the glans penis and regards them as preliminary to bone formation.

We find more detailed references in the publication of Frangenheim (1907), though this author examined only an excised preparation. The bone had a lamellar structure and at the edges there was a zone rich in cells and blood vessels which was very similar to an osteogenetic tissue, although no osteoblasts were found.

A very good description of macro- and microscopic observations is available in the publication of Furuta (1924). He examined the corpse of a 74-year-old tailor, deceased of pneumonia, and found the following: In the radix penis there was a hard, tangible structure, though the outer appearance of the penis was normal. The roentgenogram disclosed two pieces of bone, hook-shaped and crooked in the form of a letter "S", with an uneven surface; the length of the bones were 26 mm. and 34 mm.; the width 5 and 7 mm.; thickness 0.5-1.5 mm. The histological examination showed that the two thin bone plates were both localized at the dorsal side of the outer surface of the tunica albuginea. The narrow parts of the bones had a compact and lamellar structure, in the broader ones, however, Haversian canals were disclosed. These were especially large, and filled with adipose tissue, blood vessels and fibrous connective tissue. Fibro-metaplastic growth without osteoblasts were found at the ends of the bones. There were many calcium depositions at the edges of the bone plates and in the surrounding connective tissue. The author believes that the bones could surround the entire corpora cavernosa, when growing continuously... "and the bones are inclined to form a solid bony sheath, limited to the tunica albuginea."

The previously mentioned case of Vermooten (1933) was a curious one in which the glans penis of a 19-year-old man was injured by a revolver bullet. Three months later, after normal healing of the wounds, pieces of bone and cartilage developed in the glans. As the wound also involved the corpus penis, scrotum and buttock, the author asks: "Why this should have occurred in glans and nowhere else because there was no evidence, even on microscopic examination of any inflammatory process." About this case Vermooten (1933) says further: "Except in chimpanzee, ossification in the glans penis is apparently a very rare occurrence. So far we have been unable to find any human case reported in the literature."

#### DISCUSSION

The significance of the occasional presence of bone tissue in the human penis is unclarified. Chetwood (1899), Koch (1907) and others are of the opinion that the human os penis is an atavistic phenomenon. The conception, however, is too contradictory to be accepted. Let us mention only the variable location of the bone tissue, which scarcely ever coincides with the location of the os penis in animals, which are almost always placed in the area of the glans penis. On the contrary, in the human penis the bone tissue has been found sometimes in the corpus, sometimes in the radix penis, as well as in the fascia or in the tunica albuginea, and even in the area of the corpora cavernosa. Also the outer shape of the bone is not analogous with the os priapi of the Primates or other animals. A certain expedience appears in the os penis of the animals in relation to the form and location to the bone. But the bone pieces discovered in human penis are mostly flat, of about equal length and width, often curved in the shape of a hook, with uneven and notched surfaces. The same could be said concerning size. If it were a phylogenetic vestige, a rudiment, it could be expected that the human os penis would be smaller than the os penis of the apes,

or at least not exceed the latter. On the contrary, we see the reverse: the os penis of the apes is often smaller than in the human. It is evident even more distinctly from the number of the bones. The animals have only one os penis, but in the human penis the number of bones has been one, two, three, four, five or even many, as it was in the case of our preparation.

Furuta (1924) says that the pathological character of the ossification of the penis is obvious from the fact that the bone tissue does not fit organically to the form of the penis, but rather represents an impediment, especially during an erection. MacClellan (1827), Hecker (1844), Siegmund (1874), and Brohl (1904) have observed that during the erection the penis cracks because of the hard enclosure and the erections are painful. Kaufmann (1922) has noticed a curvature of the epidermis in the environs of the bone also in a lax penis. In the case described by MacClellan (1827) even the discharge of urine was painful.

Hence it ensues that the formation of a bone tissue in human penis does not cause even the least improvement of its functions. If it were an inherited phenomenon, such rudiments should be found in the penis of younger individuals as well. But the described bone pieces had been found in the penis of old and very old people only. As exception, ossification was disclosed in the penis of a 28-year-old man in the case of our own investigation, and in Vermooten's (1933) case in glans penis of a 19-year-old man. The ossification has never been found in the penis of newborns and children, nor has it been observed on several members of the same family. All these perceptions point to the idea that the process is an acquired but not a congenital occurrence. Frangenheim (1907), Furuta (1924), and Ruth (1934) have reached the same conclusion.

The question arises how these pieces of bone are originated in the penis and what is the reason thereof. It is known that the human body is able to form bone tissue or cartilage tissue in places affected by pathological events, wherever there is a connective tissue present. This process is very frequent. The bone tissue can originate even in places having nothing in common with the skeleton, for example, in the mammary gland, in the salivary gland, in the testicle, etc. Many histologists and pathologists are of the opinion that the fibroblasts are capable of transforming into the primeval embryonic condition, thus becoming able to form a new tissue. This phenomenon is defined as indirect metaplasia. In accordance with some other conception, there exists a feasibility of direct metaplasia, at least in the group of the supporting tissue, i.e., the connective tissue hyalinizes, calcifies and transforms into bone tissue or cartilage tissue, without osteoblasts appearing on the scene. According to recent ideas, there are embryonic cells among the ordinary cells of the connective tissue, which are able to form harder tissue under the influence of specific stimuli, even tissue of a kind which never appears at these places under normal conditions. This is defined as heterotypic metaplasia.

Considering the bone tissue, found in the human penis, from this angle, it can be concluded, that a metaplastic process is taking place. It is more difficult to decide to which form of metaplasia it belongs, to the heterogeneous or to the direct one. These conclusions are also in concord with the opinion of Frangen-

heim (1907) and Furuta (1924) who have conceived the ossification in the penis as a fibrometaplasia, without participation of the osteoblasts. Just as in the case described by Furuta (1924), so in our case also, the bones had a lamellar structure and a growth was discovered at the edges. By confluence of the bone plates it could come to be a complete bony cover around the entire penis, as in the case described by Merle (1899).

The question of why bone tissue appears within the connective tissue of the penis is not solved. Attempts have been made to find clues in the anamnesis, but contradictions have arisen here, too. Waelsch (cited from Furuta (1924)) tells of an induration of the connective tissue due to a chronic phlebitis and periphlebitis of the v. dorsalis penis. Tuffer (cited from Furuta (1924)) regards the os penis as a peculiar induratio penis plastica. Pelouze (1942) in his *Textbook of Urology* writes: "By plastic induration of the penis (Peyronie's disease) which is characterized by the formation of plaques of fibrous tissue, with extreme rarity there may be true bone formation. The cause of plastic induration is unknown." Siegmund (1874) had found syphilis in all cases inspected: objectively and from anamnesis. Chetwood (1899) concludes that his case resulted from diabetes. Foerster (1865) thinks that the bone tissue results from a trauma or an inflammation. Hecker (1844) is of the same opinion. He describes the case where a patient had suffered severe trauma of the penis four months before the appearance of the ossification. Therefore, he considers the os penis as a result of the traumatic inflammation. Frangenheim (1907) regards the formation of a bone tissue in the penis as resulting from a chronic inflammation, as a final stage of cavernitis or a similar process. On the contrary, Furuta (1924) informs us that no inflammation could be considered as the reason of the ossification in the case investigated by him. The author sees the basic cause for metaplasia in atherosclerosis and circulatory disturbances. He has found calcium depositions in the intima of the arteria dorsalis penis, the wall of which has been thickened and the lumen narrowed. The proposition of Furuta (1924) therefore is: in all cases of the ossification of the penis to seek for changes in the blood vessels. Hirsch (1930) in summarizing the literature concerning the human "os penis," concurs with Furuta's (1924) opinion and says: "The erectile bodies of elderly men are of favorable site for bone formation in presence of arteriosclerotic changes and inflammation." Jacoby (1924, 1925), on the contrary, denies that inflammation is the etiology and believes that arteriosclerosis is responsible.

The examination of the blood vessels in our preparation, however, showed that they are quite normal and no trace of arteriosclerosis was found. Although no direct symptoms of inflammation were found in our case, just as in Furuta's (1924), moreover blood effusions were disclosed here and there around the pieces of bone, so something pathological after all.

It is not admissible that a blood effusion is the direct cause of the metaplasia, for the pieces of bone were also found in a quite normal connective tissue. Evidently the ossification depends upon the local changes of the tissue and appears in injured spots or where metabolic disturbances are taking place.

We can assume that in our case the main stimulant which caused the favorable

preliminary condition for the formation of bone tissue has been either a trauma or a local metabolic disturbance or an intermittent pressure.

We would like to express our thanks to Dr. Elbert B. Ruth, Department of Anatomy, University of N. Dakota for critically reading this paper.

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## INTERSTITIAL CELL HYPERPLASIA OR ADENOMA

K E BLUNDON, SIMON RUSSI AND R CARL BUNTS

*From Departments of Urology and Pathology, McGuire Veterans Administration Hospital, Richmond, Va*

Interstitial cell tumor of the testis is by general agreement a rare entity, Friedman and Moore reporting a 1 per cent and Lewis an 0.8 per cent incidence in their respective large series of testicular tumors. Pathologic classification has therefore been based on the observation in a very limited number of cases and on occasion on single case findings.

To date, less than 50 cases have been reported in the literature and about 40 per cent of these have been added since 1945. Many cases have been controversial. For example, Pana's case which was reported as adenoma was substantiated by some investigators but was also called Leydig cell hyperplasia and an adrenal cortical rest by others. Shupe's case was called an adrenal cortical tumor by Karsner and also by Stewart but was accepted by the Armed Forces Institute of Pathology as interstitial cell adenoma. In tabulating the cases reported as interstitial cell tumors, almost one-third were found to have occurred in patients with atrophic testis or with cryptorchidism, although not necessarily in the same testis. However, it would seem to indicate that interstitial cell tumor is often found in conjunction with decreased spermatogenesis.

The normal histologic and physiologic pattern of Leydig cells has been described in some detail. The vacuolated polyhedral Leydig cells, which are believed to be derived from primordial mesenchymal cells, are usually found interspersed in groups of ten to twelve cells in the loose connective tissue between the seminiferous tubules and are said to comprise some 12 per cent of the bulk of the adult testis. Cytologically these cells are distinguishable by their large eccentric vesicular nuclei, a heavy brown intracellular pigment, and heavy deposits of lipid. This lipid is believed to be the androgenic hormone or a precursor thereof and, according to Lynch and Scott, assumes maximum concentration in the years of greatest sexual activity. Androgenic hormone is excreted in the urine as 17-ketosteroids. In the male about three-eighths of the 17-ketosteroid output is derived from the testis with five-eighths coming from adrenal cortical hormone metabolites. Theoretically at least, one is inclined to believe that 17-ketosteroid output should be increased in either Leydig cell hyperplasia or in true tumor. This determination has been listed in only six cases, in four of which it was elevated. Leydig cell hyperplasia of varied degree is of fairly common occurrence and occurs as sheets of cells resembling liver cells or adrenal cells interspersed between seminiferous tubules.

Interstitial cell hyperplasia is an apparently normal finding in the testis of senility. It is known to occur in cryptorchidism with debated frequency and is

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Accepted for publication May 27 1952

often described as an autopsy finding in such debilitating diseases as tuberculosis, syphilis, pernicious anemia and carcinoma. Hyperplasia has also been induced by a number of other conditions such as x-ray radiation, estrogens, vitamin E deficiency and vasectomy.

The generally accepted criteria for differentiation of a Leydig cell adenoma from hyperplasia are:

1) Encapsulation: Adenomas are usually encapsulated or at least distinctly demarcated from the host tissue.

2) Displacement of the host tissue and absence of seminiferous tubules scattered throughout the lesion.

Tabulation of pathologic characteristics in cases reported to date indicates that almost 50 per cent of cases reported as tumor can not be differentiated from hyperplasia by present morphologic criteria. One might categorically

TABLE 1. *Tabulation of clinical findings in interstitial cell tumors*

|           | TOTAL CASES | GYNecomASTIA | ATROPHY OR<br>CRYPTORCHIDISM | INCREASED<br>17-KETOSTEROID |
|-----------|-------------|--------------|------------------------------|-----------------------------|
| Children* | 13          | 1            | 3                            | 1                           |
| Adults    | 32          | 3            | 10                           | 3                           |
| Total     | 45          | 4            | 13                           | 4                           |

\* All children showed precocious puberty, macrogenitalism and skeletal maturation.

TABLE 2

|                           | PRESENCE | ABSENCE | NOT MENTIONED |
|---------------------------|----------|---------|---------------|
| Capsule                   | 23       | 12      | 10            |
| Interspersed sem. tubules | 19       | 17      | 9             |

classify such cases as hyperplasia had they not often clinically presented such marked endocrinologic changes or even metastases.

The only valid criterion of malignancy is apparently the presence of metastases. Benign lesions cannot be differentiated from malignant ones morphologically. Eight out of 45 cases develop metastases.

The difficulty in differentiating true interstitial cell adenoma from hyperplasia in a case recently under our care stimulated the review of differential criteria for the diagnosis of interstitial cell adenoma, carcinoma or hyperplasia.

#### CASE REPORT

A 27 year old white man was first admitted to McGuire V. A. Hospital on October 31, 1950, free of symptoms. A tumor of the right testis had been discovered 3 months before admission in the course of a physical examination for employment. Immediate orchiectomy had been advised at that time, but the patient had procrastinated. Despite the lapse of 3 months before reporting to the hospital, the patient had remained symptom free and the testis had not

TABLE 3. *Pathologic characteristic of interstitial cell tumor*

| NAME                                 | CAPSULE | INTERSPERSED<br>SEM TUBULES | INTRACELL<br>LIPOID | METASTASES |
|--------------------------------------|---------|-----------------------------|---------------------|------------|
| Sacchi, 1895                         | ×       | ×                           | ×                   |            |
| Chevassu, 1906                       | 0       | +                           | +                   |            |
| Kaufman, 1908                        | +       | ±                           | +                   |            |
| Kaufman, 1908                        | +       | ±                           | +                   |            |
| Masson and Sencert, 1923             | +       | ±                           | +                   |            |
| De Josselin De Jong, 1926            | 0       | 0                           | +                   | +          |
| Rowlands and Nicholson, 1929         | +       | ±                           | +                   |            |
| Pitrolffy-Szabo, 1938                | +       | ×                           | +                   |            |
| Pana, 1931                           | +       | ±                           | +                   |            |
| Rigoletti, 1936                      | +       | 0                           | +                   |            |
| Stewart, Bell, Roehlke, et al., 1936 | 0       | +                           | 0                   |            |
| Hunt and Budd, 1939                  | +       | 0                           | +                   |            |
| Jemerin, 1937                        | +       | 0                           | +                   |            |
| Braun, 1939                          | ×       | ×                           | 0                   |            |
| Huffman, 1941                        | 0       | 0                           | +                   |            |
| Somerford, 1941                      | ×       | 0                           | +                   |            |
| Warren, S and Olshausen, 1932        | 0       | 0                           | ×                   |            |
| Masson and Venning, 1942             | ×       | ×                           | ×                   | +          |
| Bonser and Hawksley, 1943            | +       | 0                           | ×                   |            |
| Bonser and Hawksley, 1943            | +       | ±                           | +                   | +          |
| Rezek, 1943                          | ×       | ×                           | ×                   |            |
| Masson, 1943                         | ×       | ×                           | ×                   | +          |
| Demirleau, et al, 1943               | +       | 0                           | ×                   | +          |
| Nation, et al, 1944                  | +       | ±                           | +                   |            |
| Nation, et al, 1944                  | +       | ±                           | +                   |            |
| Nation, et al, 1944                  | 0       | ±                           | +                   |            |
| Neeve and Marsh, 1944                | +       | ×                           | ×                   |            |
| Werner, 1944                         | +       | ±                           | 0                   |            |
| Ranstrom, 1945                       | +       | 0                           | 0                   |            |
| Anderson, 1946                       | ×       | 0                           | 0                   |            |
| Wilbur and Burger, 1948              | 0       | ±                           | 0                   |            |
| Price, 1948                          | ×       | ×                           | +                   |            |
| Sandblom, 1948                       | +       | ±                           | 0                   |            |
| Scully and Parham, 1948              | +       | ×                           | 0                   |            |
| Reiners and Horn, 1949               | +       | 0                           | ×                   |            |
| Melnicow, et al, 1949                | +       | 0                           | ×                   |            |
| James and Shupe, 1950                | 0       | 0                           | 0                   |            |
| Fraser, 1950                         | 0       | +                           | 0                   |            |
| Gharpure, 1950                       | 0       | 0                           | +                   | +          |
| Garvey and Daniel, 1951              | ×       | ±                           | ×                   |            |
| Grabstald, et al, 1951               | +       | 0                           | +                   |            |
| Flynn and Severance, 1951            | +       | ±                           | +                   |            |
| Tedeschi and Burke, 1951             | 0       | 0                           | +                   | +          |
| Authors                              | 0       | ±                           | +                   |            |
| Christeson and Nettleship, 1952      | ×       | +                           | 0                   |            |

Present = +

Absent = 0

Few = ±

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often described as an autopsy finding in such debilitating diseases as tuberculosis, syphilis, pernicious anemia and carcinoma. Hyperplasia has also been induced by a number of other conditions such as x-ray radiation, estrogens, vitamin E deficiency and vasectomy.

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TABLE 1. *Tabulation of clinical findings in interstitial cell tumors*

|           | TOTAL CASES | GYNecomASTIA | ATROPHY OR<br>CRYPTORCHIDISM | INCREASED<br>17-KETOSTEROID |
|-----------|-------------|--------------|------------------------------|-----------------------------|
| Children* | 13          | 1            | 3                            | 1                           |
| Adults    | 32          | 3            | 10                           | 3                           |
| Total     | 45          | 4            | 13                           | 4                           |

\* All children showed precocious puberty, macrogenitalism and skeletal maturation

TABLE 2

|                           | PRESENCE | ABSENCE | NOT MENTIONED |
|---------------------------|----------|---------|---------------|
| Capsule                   | 23       | 12      | 10            |
| Interspersed sem. tubules | 19       | 17      | 9             |

classify such cases as hyperplasia had they not often clinically presented such marked endocrinologic changes or even metastases.

The only valid criterion of malignancy is apparently the presence of metastases. Benign lesions cannot be differentiated from malignant ones morphologically. Eight out of 45 cases develop metastases.

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TABLE 3 *Pathologic characteristic of interstitial cell tumor*

| NAME                                | CAPSULE | INTERSPERSED<br>SEM TUBULES | INTRACELL<br>LIPOID | METASTASES |
|-------------------------------------|---------|-----------------------------|---------------------|------------|
| Sacchi, 1895                        | ×       | ×                           | ×                   |            |
| Chevassu, 1906                      | 0       | +                           | +                   |            |
| Kaufman, 1908                       | +       | ±                           | +                   |            |
| Kaufman, 1908                       | +       | ±                           | +                   |            |
| Masson and Sencert, 1923            | +       | ±                           | +                   |            |
| De Josselin De Jong, 1926           | 0       | 0                           | +                   | +          |
| Rowlands and Nicholson, 1929        | +       | ±                           | +                   |            |
| Pitroff-Szabo, 1938                 | +       | ×                           | +                   |            |
| Pana, 1931                          | +       | ±                           | +                   |            |
| Rigoletti, 1936                     | +       | 0                           | +                   |            |
| Stewart, Bell, Roehlke, et al, 1936 | 0       | +                           | 0                   |            |
| Hunt and Budd, 1939                 | +       | 0                           | +                   |            |
| Jemerin, 1937                       | +       | 0                           | +                   |            |
| Braun, 1939                         | ×       | ×                           | 0                   |            |
| Huffman, 1941                       | 0       | 0                           | +                   |            |
| Somerford, 1941                     | ×       | 0                           | +                   |            |
| Warren, S and Olshausen, 1932       | 0       | 0                           | ×                   |            |
| Masson and Venning, 1942            | ×       | ×                           | ×                   | +          |
| Bonser and Hawksley, 1943           | +       | 0                           | ×                   |            |
| Bonser and Hawksley, 1943           | +       | ±                           | +                   | +          |
| Rezek, 1943                         | ×       | ×                           | ×                   |            |
| Masson, 1943                        | ×       | ×                           | ×                   | +          |
| Demerleau, et al, 1943              | +       | 0                           | ×                   | +          |
| Nation, et al, 1944                 | +       | ±                           | +                   |            |
| Nation, et al, 1944                 | +       | ±                           | +                   |            |
| Nation, et al, 1944                 | 0       | ±                           | +                   |            |
| Neeve and Marsh, 1944               | +       | ×                           | ×                   |            |
| Werner, 1944                        | +       | ±                           | 0                   |            |
| Ranstrom, 1945                      | +       | 0                           | 0                   |            |
| Anderson, 1946                      | ×       | 0                           | 0                   |            |
| Wilbur and Burger, 1948             | 0       | ±                           | 0                   |            |
| Price, 1948                         | ×       | ×                           | +                   |            |
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| Scully and Parham, 1948             | +       | ×                           | 0                   |            |
| Reiners and Horn, 1949              | +       | 0                           | ×                   |            |
| Metcow, et al, 1949                 | +       | 0                           | ×                   |            |
| James and Shupe, 1950               | 0       | 0                           | 0                   |            |
| Fraser, 1950                        | 0       | +                           | 0                   |            |
| Gharpure 1950                       | 0       | 0                           | +                   | +          |
| Garvey and Daniel, 1951             | ×       | ±                           | ×                   |            |
| Grabstald et al, 1951               | +       | 0                           | +                   |            |
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| Tedeschi and Burke, 1951            | 0       | 0                           | +                   | +          |
| Authors                             | 0       | ±                           | +                   |            |
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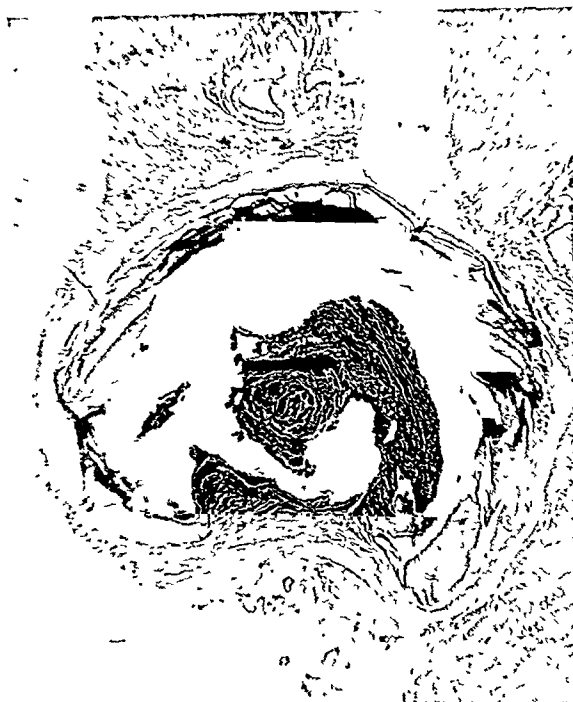


FIG 2. Photograph of small ossified shell with central cystic area filled with laminated keratin.  $\times 15$

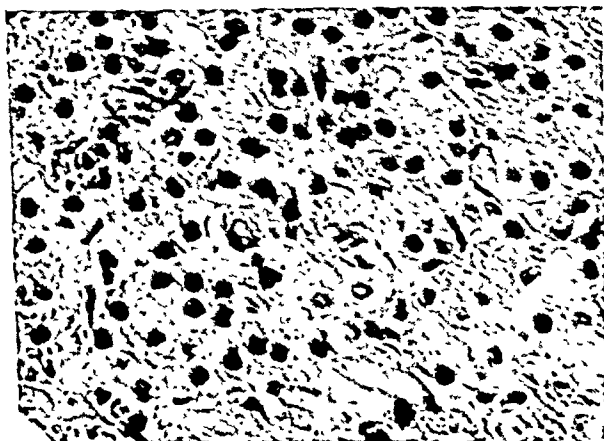


FIG 3 Showing massive proliferation of interstitial cells arranged in cords and lobules.  $\times 100$

simple epidermoid cyst filled with keratin and lined by compressed squamous stratified epithelium. The epithelium was supported by a dense layer of hyalinized connective tissue. The hard nodule afore-mentioned was made up of a well localized crescent-shaped focus of ossification (fig. 2). In the central portion of

significantly enlarged in the interim. Although bilateral testicular atrophy had been present as long as the patient could remember, there was no history of mumps, orchitis, or injury. Puberty had been delayed to the age of fifteen and body hair and beard had been sparse. Libido had been virtually absent until the age of twenty-four, after which normal sexual drive had apparently been present.

Physical examination showed a tall, eunuchoid male, 6 feet 1½ inches tall, weighing 146 pounds. The beard was very sparse. The voice was normal in timbre. The lungs were clear and there was no gynecomastia present. No abdominal masses were present. Both testes were in the scrotum. The right testis was about two-thirds normal size and was hard and somewhat nodular. The left testis was about one-fourth normal size but of normal configuration. The penis and pubic hair were normal in development and prostate was of normal size and consistency.



FIG. 1. Photograph of resected testicle

The laboratory examinations, including the Friedman test, 17-ketosteroids excretion, radiogram of the chest and excretory urogram, were all within normal range. Radiographic examination of the sella turcica revealed no findings suggestive of pituitary tumor. A simple right orchietomy was performed in November 1950 through an inguinal incision.

The capsule of the testis was smooth, gray, glistening and uniformly tense. A few delicate tortuous vessels radiated from the hilar portion of the testis (fig. 1). The cut surface revealed an eccentrically placed ovoid cyst filled with pale yellow crumbling material. At one pole of the cyst was a hard, small nodule which cut with resistance suggesting calcification. Between the periphery of the cyst and the tunica albuginea was a layer of orange-yellow tissue varying from 1 to 5 mm. in thickness.

Microscopic examination of multiple segments of the specimen revealed a

the course of years, due to distention by desquamated keratin and subsequently extruded from its bony cage compressing and displacing the host tissue. The orange-yellow layer between the wall of the cyst and the tunica albuginea was made up of cellular tissue arranged in lobules and cords in a manner resembling the pattern of liver parenchyma (fig. 3). The individual cells had an eosinophilic cytoplasm which in some of the cells was vacuolated containing sudanophilic material and in some others was impregnated with a fine brown pigment (fig. 4). The nuclei were fairly uniform in size and staining intensity. The shapes of the nuclei varied from round to short ovals and some showed a wrinkled nuclear membrane. Some contained prominent punctate nucleoli. There was no evidence of invasive tendencies, pleomorphism or mitotic activity. Occasional seminiferous tubules in various stages of atrophy and hyalinization were scattered through the tissue (fig. 5).

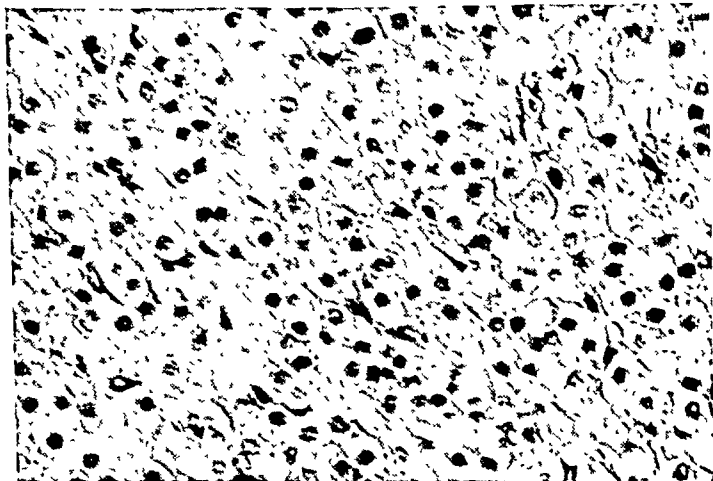


FIG. 6. Biopsy from contralateral testis showing proliferation of interstitial cells identical in appearance with lesion in other testis.

The postoperative course was uncomplicated and follow-up 15 months after orchiectomy has revealed no evidence of local recurrence or metastases.

Six months after the first operation a sperm count was performed to determine the degree of spermatogenesis that was present in the remaining atrophic testis. Complete azospermia was found. A biopsy of the remaining testis revealed masses of Leydig cells assuming the same pattern as in the removed testis (fig. 6).

#### DISCUSSION

We should like to limit the discussion of the adult teratoma as it presented little difficulty in diagnosis and due to the mature components offered a favorable prognosis.

We are puzzled, however, by the peculiar proliferation of the interstitial cells, which poses the following problems: 1) Is it a true tumor or hyperplasia? 2) If it is a tumor, is it benign, malignant or potentially malignant?; and 3) the

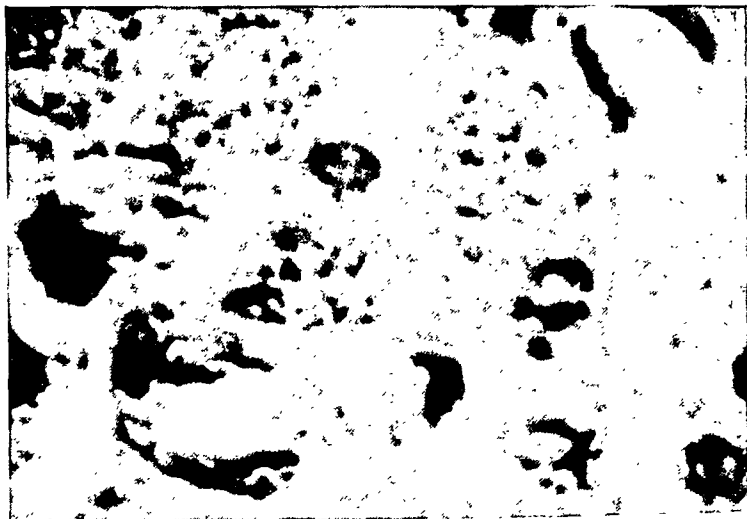


FIG. 4. Showing granular pigment in cytoplasm of interstitial cells.  $\times 440$

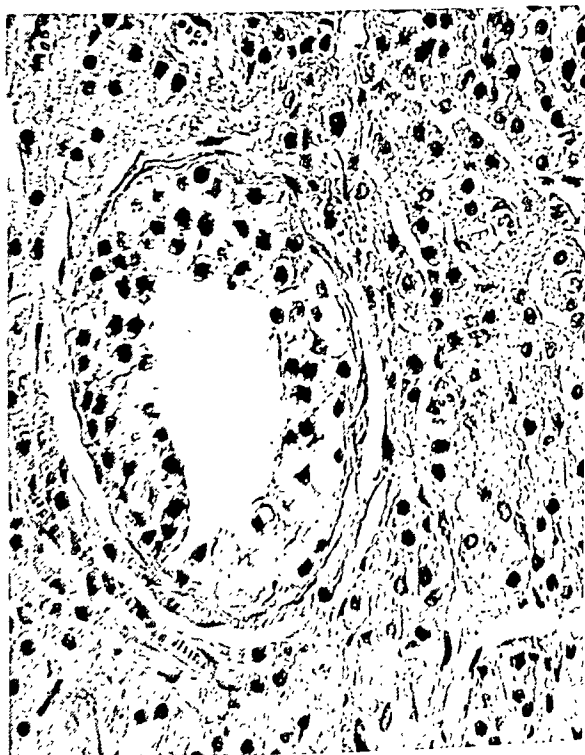


FIG. 5. Showing section of seminiferous tubule surrounded by masses of interstitial cells.  $\times 200$

the bone was a minute cystic area which was apparently a recess of the large epidermoid cyst. We interpreted this finding as an adult teratoma made up of a peripheral layer of bone and a central epidermoid cyst. The cyst expanded in

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practical question, should the contralateral testicle be removed or treated otherwise? To answer the first question, whether the lesion in our case is an adenoma or diffuse hyperplasia, we reviewed the postulates for differentiation. An adenoma should be an encapsulated or at least a discrete lesion displacing the host tissue. In our case there was a diffuse numerical increase of interstitial cells with almost total replacement of the spermatogenic elements of the gonad. The only barriers were the tunica albuginea and the wall of the cyst. Another criterion is absence of seminiferous tubules within the adenoma. In our case the seminiferous tubules, however scanty and atrophic, were scattered here and there throughout the lesion.

One argument in favor of hyperplasia versus tumor is the presence of a bilateral lesion. It seems improbable for one man to develop three tumors in two testicles. We realize that this point is based more on conjecture rather than of fact.

To answer the second question whether the lesion is benign or malignant we have to assume that it is a tumor in spite of the fact that it does not exactly fit the postulates stated above. We have no criteria to determine its benign or malignant character. All of the eight previously reported cases which developed metastases had the same morphologic features as benign tumors, and three of the eight could not be differentiated morphologically from hyperplasia. Metastases may occur as late as 10 years after the removal of the primary lesion.

To answer the third question as to the treatment of the other testicle we are inclined to withhold x-ray therapy. Warren as well as Best and Taylor found that interstitial cells are radioresistant. Kyrle has actually induced hyperplasia by radiation. The advisability of the surgical removal of the other testis hinges on the debatable pathological classification of the first testis. In addition to our own studies, we sought and obtained the help of several consultants in several medical centers. The opinions of the consultants were divided, however, between the diagnosis of interstitial cell adenoma and hyperplasia. The diagnosis of adenoma for the most part was preferred.

#### SUMMARY AND CONCLUSIONS

A case of bilateral diffuse proliferation of Leydig cells associated with a unilateral teratoma of the testicle is presented.

It is believed that there is no sharp definite line of demarcation separating neoplasia from hyperplasia in cases of massive interstitial cell proliferation.

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prevented further examination. A hard mass could be felt in the left lower quadrant of the abdomen.

Proctoscopic examination was very painful and therefore not very satisfactory. A bleeding granulomatous mass was seen in the upper part of the rectum, suspicious of a new growth. X-ray after barium enema showed a defect high in the rectum and a narrowing in the sigmoid. X-ray studies showed the kidneys to be of normal size and position. Psoas shadows and osseous structures were normal and distinct. There was no evidence of urinary calculi or metastases.

Laboratory examination was as follows: Urinalysis: pH 5.5, no sugar or albumin, 8 to 9 white blood cells and few calcium oxalate crystals. The hemoglobin was 85 per cent, white blood cells 10,450, and red blood cells 4,360,000. The differential count showed 71 segmented, 17 lymphocytes, 7 stab forms, 2 juveniles, and 3 eosinophiles. Nonprotein nitrogen 44.0 mg., creatinine 1.85 mg., urea nitrogen 21.0, sedimentation rate 8 in 15 minutes, 41 in the hour. An Aschheim-Zondek test was negative. X-ray film of the chest showed no evidence of tumor.

On June 9, operation was performed by J. I. Waller. Under spinal anesthesia an incision was made through the right inguinal region into the scrotum exposing the testicle and exposing the cord up to the internal abdominal-inguinal ring. The testicle was found to be in part of soft consistency and in part to be very hard and nodular. All along the cord there was great increase in size. There were hard nodular areas all the way up the cord, extending into the internal ring. Upon opening of the abdominal cavity through the inguinal ring by incision, ascitic fluid exuded, estimated to be from 3000 to 4000 cc. The palpating finger through the inguinal ring could feel greatly enlarged retroperitoneal lymph nodes along the aorta. The cord was ligated with chromic catgut and doubly tied. The right testis and cord were then removed completely up to the internal ring. A gland was also removed for biopsy. A Penrose drain was placed in the incision and the skin was closed with interrupted mattress sutures.

The gross specimen consisted of the contents of the right half of the scrotum. The mass was roughly hockey-club shaped, and the testis was surrounded with a tumor which extended along the spermatic cord. The external surface was smooth and covered with a fibrous capsule. The consistency was extremely hard. Cut section revealed a small normal looking testis which measured 3 by 2.5 cm., and which was surrounded with a thick hard tumor mass that also included the epididymis. At the base a yellowish-brown necrotic area was found in the tumor. The coarse nodular mass extended upward for 10 cm., but the spermatic cord and venous plexus were not included in the tumor mass.

Microscopic examination: In several sections of the testis no tumor tissue could be found. Most of the tubules were atrophic, had a hyaline basement membrane and only one layer of large round cells with light stained foamy cytoplasm. The Leydig cells of the interstitial tissue were not increased. Section of the tunica vaginalis adjacent to the testis revealed solid sheets and strands of dark stained cells. The tumor cells were of rather large size and they had oval nuclei very dark stained, without distinct nucleolus. The cytoplasm was very indistinct;

## CANCER OF THE TUNICA VAGINALIS: REVIEW OF LITERATURE AND REPORT OF ONE CASE

J. I. WALLER AND C. A. HELLWIG

*From the Department of Urology and Pathology, Hertzler Clinic and The Hertzler Research Foundation, Halstead, Kansas*

Extratesticular tumors of the scrotum are extremely rare. The majority of the reported cases were of benign nature. The following case of cancer of the tunica vaginalis which we recently observed in the Hertzler Clinic seems worth reporting: first, because of the great rarity of extratesticular tumors; second, to bring out the fact that tumors in or near the testis have to be regarded as malignant until proved otherwise, and third, to show the difficulty of differentiating histologically between primary and metastatic growth when a complete autopsy is not available.

### CASE REPORT

F. A., a 36 year old white man, was admitted to the hospital with the complaint of a hernia in the lower right groin of 4 months' duration. He noticed a swelling in the area of the right pubic crest, with no change in size, for 2 months before admittance. He had had no pain in this area, but tenderness was present around the testicle. There was no redness in the area. In the morning of the day he was admitted, the patient noticed that when the scrotum was pulled up the swelling decreased in size but did not disappear.

History was negative for diphtheria, typhoid, scarlet fever, and rheumatic fever. The patient was allergic against pollen but not against food. He had had a left inguinal hernia repair for strangulated hernia in 1944. The right great toe was lost at the age of 16 due to a gunshot wound. For 3 months previous to admittance the patient had had great irregularity in bowel movement and at times was constipated for 5 to 6 days. However he had had no red or black colored stool. He had lost 12 pounds of weight during these 3 months. The patient's father was living and well at 72 years of age. The mother died at the age of 57 of unknown cause. The patient was an only child, married at age 25, and had no children.

Physical examination revealed a blood pressure of 110 systolic and 70 diastolic. The heart was not enlarged; there were no murmurs noticed. The abdomen was distended. The liver and spleen were not palpable due to lack of relaxation and ascites. The left testis could be palpated in the left lower quadrant just above a healed incision. The testis measured 3 by 5 cm., was oval in shape and rubbery in consistency. The left testis was not in the scrotum. The right testis had a mass in the upper pole which was round, hard, measured 3 by 3 cm. and was continuous with a mass running along the spermatic cord which was tear-shaped and with a sharp edge dipping into the external abdominal ring. The consistency was hard. The lower half of the right testis was tender to touch. The penis was not unusual. Rectal examination revealed a good sphincter tone. A hard mass in the posterior part, just beyond the sphincter, occupying the entire lumen

tumor is an endothelioma or mesothelioma originating from the surface layer of mesothelial cells. We could not support the diagnosis of sympathicoblastoma of one consultant as we did not find rosette formation or nerve processes. We believe that the malignant part of the tumor is epitheliomatous, and Stout's ex-

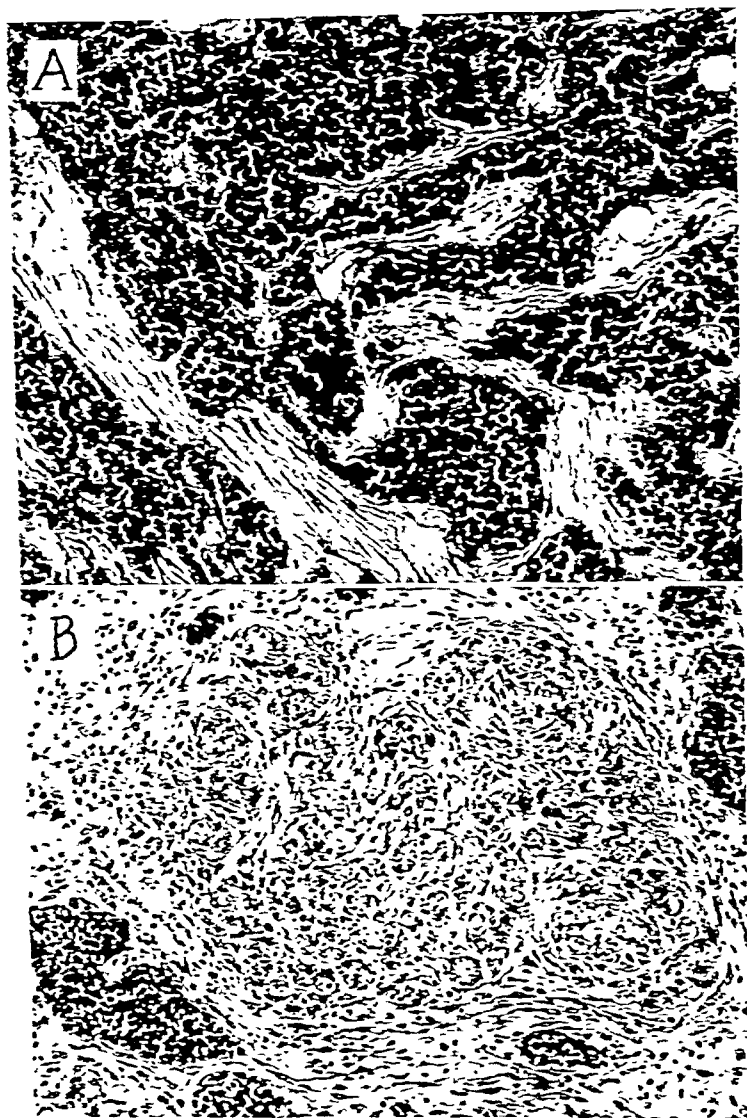


FIG. 2 A. solid carcinoma of tunica vaginalis composed of interlacing strands of tumor cells B. tumor of tunica vaginalis resembling area of hemangioendothelioma.  $\times 140$

planation seems most plausible, namely that this tumor is an embryonal carcinoma originating from some of the embryonal genito-urinary cell rests which are so often found in the region.

In favor of this view would be the striking radio-sensitivity of the retro-

no cell borders could be recognized. The cells were not arranged in glandular structures, and no rosette formation could be seen. No processes or nerve fibers could be demonstrated as originating from the tumor cells. In several areas, lumens of varying size and form were seen. The cells lining the internal surface had the appearance of hypertrophic endothelial cells. In many spaces in the wall, button-like protrusions composed of tumor cells were noticed. In one section an angioma-like proliferation of capillaries was noticed. The sections of the epididymis did not reveal tumor tissue between or within the tubules, which had columnar epithelium. No teratomatous elements were found in the tumor. Our histological diagnosis was solid carcinoma of the tunica vaginalis.



FIG. 1. Tumor of tunica vaginalis extending to inguinal ring. Cross section shows extra-testicular location of tumor.

Microscopic sections of this tumor were submitted to well known pathologists in Philadelphia, Kansas City, Missouri, Temple, Texas, New York City and Washington, D. C. The following histological diagnoses were returned: 1) Metastatic sympathicoblastoma; 2) metastasis of oat cell carcinoma of lung or primary mesothelioma; 3) grade 4 angio-endothelioma (angiosarcoma); 4) embryonal carcinoma, originating in embryonal genito-urinary remnants; 5) malignant mesothelioma or myosarcoma.

Three of the authorities, therefore, favored a primary tumor, two a metastatic growth. Three regarded the tumor as a sarcoma, and two as a carcinoma.

A complete physical examination, including x-ray study of the lungs and gastro-intestinal tract, did not reveal any primary tumor in our case, and we assume that the tumor originated in the tunica vaginalis. The fact that the nodular tumor masses in the lymph spaces showed a thin layer of endothelium continuous with the interior surface of the lymph spaces, makes it questionable that the

tumor is an endothelioma or mesothelioma originating from the surface layer of mesothelial cells. We could not support the diagnosis of sympathicoblastoma of one consultant as we did not find rosette formation or nerve processes. We believe that the malignant part of the tumor is epitheliomatous, and Stout's ex-

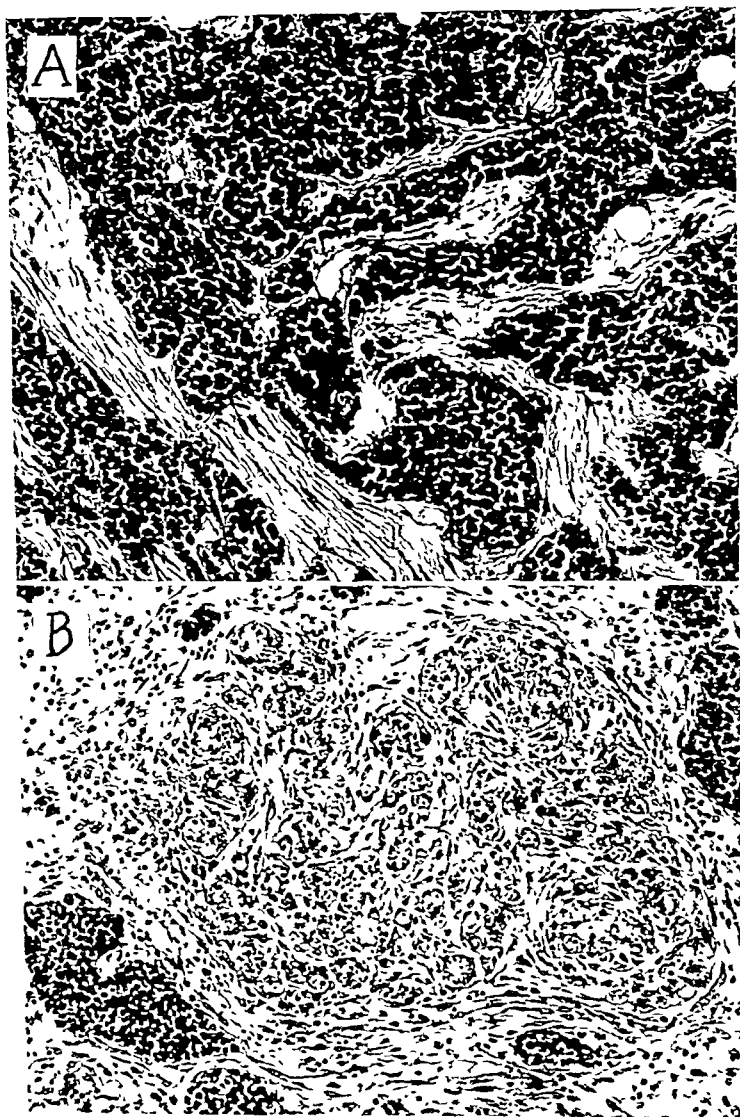


FIG. 2 A, solid carcinoma of tunica vaginalis composed of interlacing strands of tumor cells B, tumor of tunica vaginalis resembling area of hemangioendothelioma.  $\times 140$

planation seems most plausible, namely that this tumor is an embryonal carcinoma originating from some of the embryonal genito-urinary cell rests which are so often found in the region.

In favor of this view would be the striking radio-sensitivity of the retro-

peritoneal metastases. Today, 3 months after operation, the patient appears in perfect health. He is working as actively as before his disease, his ascites is completely gone, and he has no gastro-intestinal symptoms.

If we accept Stout's interpretation that this tumor of the tunica vaginalis is dysontogenetic, then it should show the same characteristics as do solid carcinomas of the testis. From a histologic study of 50 malignant tumors of the testis we concluded that all common malignant testicular tumors are of teratomatous nature and that solid testicular carcinoma often contains tissue other than epithelium, namely, islands of muscle, cartilage, and myxomatous tissue. Hamburger, Bang and Nielson<sup>1</sup> called this type of testicular tumors mixed epithelioma, the same as the embryonal carcinoma of other writers.



FIG. 3. Subendothelial bud of tumor cells in wall of large mesothelial space, resembling mesothelioma

While in our case the carcinomatous elements predominated, the presence of angiomatous, myomatous, and neurocytic elements besides the solid carcinoma led some of the consultants to the diagnosis of myosarcoma, angiosarcoma and neuroblastoma. We believe that all these elements are derivatives of multipotent embryonal cells and that in this dysontogenetic tumor the malignant elements were of epithelial nature, while benign mesenchymal and neurogenic elements were also present and derived from the same mother cells.

Postoperative course: The operative wound healed by primary union and the patient was dismissed on June 23. He received deep x-ray therapy to the lower abdomen from June 17 to June 24, a daily dose of 50-200-25-360 r, and a total of 2950 r. He was examined in the clinic on July 28, 1952. His right shoulder

<sup>1</sup> Hamburger, C., Bang, F. and Nielson, J. *Acta. path. et microbiolog. Scandinav.* 13: 75, 1936

had been hurting for a few days, otherwise he was feeling fine. He had a good appetite and the bowels were normal. The abdomen was soft on examination and there was no evidence of recurrence. No enlargement of the inguinal lymph nodes was noticed.

#### DISCUSSION

Our case belongs to the rare group of malignant tumors of the tunica vaginalis, of which Thompson<sup>2</sup> could collect only 17 cases from the literature. According to this author, it is often very difficult and sometimes practically impossible to distinguish tumors of the tunica vaginalis from those arising in adjacent structures. The majority of the tumors were benign.

Rubaschow<sup>3</sup> collected reports of 15 cases of sarcoma of the tunica vaginalis and to these only two were added by Thompson; one a case of sarcoma in a 17 year old patient reported by Valdoni,<sup>4</sup> and a case of fibrosarcoma reported by Donati.<sup>5</sup> In 11 cases listed by Rubaschow the oldest patient was only 35 years old, and the majority of the tumors occurred in very young individuals. In Thompson's own series of 41 extratesticular tumors, only 2 cases originated in the tunica vaginalis and both were benign.

Hinman and Gibson<sup>6</sup> accepted 12 reports of sarcoma of the tunica vaginalis. The earliest reference is a case reported by Home<sup>7</sup> and accepted as probably sarcoma by Curling,<sup>8</sup> in which the operation was performed by Hunter in 1782. Curling cites the unusual case of Craven,<sup>9</sup> in a man of 45 years, with rapid swelling of the scrotum of two months' duration. The tumor and both testicles were removed. The patient died a few months later of internal disease, probably of metastases. Curling and Klebs<sup>10</sup> believed this to be a case of double diffuse sarcoma of the tunica vaginalis.

Adler,<sup>11</sup> in 1894, reported a large sarcoma of the tunica vaginalis of 3 weeks' duration in a boy of 19 years, and Reverdin,<sup>12</sup> in the same year, reported a case in an infant. Miyata<sup>13</sup> (1913) reported 3 cases which Schultz<sup>14</sup> and Eisendrath believe may be accepted. Kocher,<sup>15</sup> in 1887, reported a myxosarcoma of the tunica vaginalis in a boy of 19 years.

An unusual case is recorded by Karewski<sup>16</sup> in a patient of 57 years, in which the tumor weighed 8,900 gm. A tumor in the region of the right testicle had been present since childhood and had started to grow rapidly, the scrotum reaching

<sup>2</sup> Thompson, G. J.: *Surg., Gynec. & Obst.*, 62: 712, 1936.

<sup>3</sup> Rubaschow, S.: *Arch. f. klin. Chir.*, 141: 14, 1926.

<sup>4</sup> Valdoni, P.: *Policlinico (sez. chir.)*, 34: 244, 1927.

<sup>5</sup> Donati, D.: *Arch. ital. di urol.*, 11: 472, 1934.

<sup>6</sup> Hinman, F. and Gibson, T. E.: *Arch. Surg.*, 8: 100, 1924.

<sup>7</sup> Home: *Observations on Cancer*. 1805, p. 125.

<sup>8</sup> Curling: *Tr. New York. Path. Soc.*, 1: 119, 1881-1882.

<sup>9</sup> Craven: Quoted by Curling.

<sup>10</sup> Klebs: *Pathol. Anat.*, 1: 1071, 1885.

<sup>11</sup> Adler: *Semaine méd.*, 2: 320, 1894.

<sup>12</sup> Reverdin: *Rev. méd. de la Suisse Rom.*, 1894, No. 4.

<sup>13</sup> Miyata: *Arch. f. klin. Chir.*, 101: 426, 1913.

<sup>14</sup> Schultz, O. T. and Eisendrath, D. N.: *Arch. Surg.*, 2: 493, 1921.

<sup>15</sup> Kocher: *Deutsch. Chir.*, 1887, p. 183.

<sup>16</sup> Karewski: *Semaine méd.* p 314 (July) 1894.



to his knees. Clinically the case is one of a benign fibroma undergoing malignant degeneration.

In Grote's<sup>17</sup> case, in a man of 30 years, the tumor weighed 150 gm. and was from 6 to 8 years' duration. Most of the growth had occurred during the last 2 years. At operation the parietal layer of the tunica vaginalis was found to consist of multiple nodules, which on microscopic examination proved to be a fibrosarcoma. The patient was living and well 2 years later.

Dudon<sup>18</sup> reported a questionable case of carcinoma which Grote regards as sarcoma. Rindone<sup>19</sup> (1901) has reported a tumor originating in the tunica vaginalis which he regards as a lymphangio-endothelioma.

In 1937, Darget and Penaud<sup>20</sup> reported a malignant tumor of the tunica vaginalis simulating a hydrocele. The patient was a 29 year old man who had a swelling in the right scrotum. It was the size of a fist and was clear on transillumination. At operation a hydrocele was found with pink granulations covering the internal surface of the hydrocele sac. The testis was normal. The tumor was histologically an adenocarcinoma corresponding to the formerly called wolffian tumors. The authors accept Chevassu's explanation that these carcinomatous tumors originate from embryonal nests embedded in the region near the testicle or epididymis.

In 1941, Gräflin<sup>21</sup> collected from the world literature 48 cases of sarcoma originating in the tunica vaginalis, and added his own case of mesenchymal mixed tumor. Fritzler<sup>22</sup> observed a polymorphous cell sarcoma weighing 440 gm., in a 46 year old man. A case of myosarcoma of the tunica vaginalis in a 5 year old boy was described by Trabucco in 1940.

N. C. Foote<sup>23</sup> has seen one case of malignant mesothelioma of the tunica in an old man. The tumor, 10 by 15 cm. in diameter, arose from the epididymis and was overlying an atrophic testis which was uninvolved. The patient died from multiple metastases. Microscopic study showed solid masses of undifferentiated cells growing in alveolar spaces and apparently representing malignant transformation of a mesothelioma. Mitoses were abundant.

Willis's<sup>24</sup> report entitled "A Metastatic Deposit of Bronchial Carcinoma in a Hydrocele Misdiagnosed 'Endothelioma'" makes one wary to accept any primary tumor of the tunica vaginalis except when a complete autopsy has excluded a primary tumor elsewhere. Willis's patient was a 74 year old man who had a tumor of the tunica vaginalis associated with a large hydrocele. At first Willis regarded the growth, though of carcinomatous appearance in some areas, as endothelioma arising from the cells of the tunica vaginalis. At autopsy 16 months after operation, a small carcinoma arising in a main bronchus of the upper left lung lobe was found. This, Willis regards as the primary source of the tumor in the hydrocele sac.

<sup>17</sup> Grote: Ueber Geschwulste der Tunica vaginalis propria. Inaug. Diss., Gottingen, 1908.

<sup>18</sup> Dudon: Bordeaux méd., 1873, p. 259.

<sup>19</sup> Rindone: Gior. d. Ass., napol. di med. e nat., 1901, p. 280.

<sup>20</sup> Darget, R. and Penaud: Bull. Soc. franç. d'urol., p. 201, (July 5) 1937.

<sup>21</sup> Gräflin, G.: Helvet. Med. acta, 8: 336, 1941.

<sup>22</sup> Fritzler, Kurt: Arch. f. klin. Chir., 19: 271, 1925.

<sup>23</sup> Foote, N. C.: N. Y. J. Med., 49: 234, 1949.

<sup>24</sup> Willis, F. A.: J. Path. & Bact., 47: 35, 1938.

## SUMMARY

Extratesticular tumors of the scrotum are extremely rare. A case of primary cancer of the tunica vaginalis is reported in a 36 year old man. He is well 3 months after operation and deep x-ray therapy.

Tumors in or near the testis must be regarded as malignant until proved otherwise.

The difficulty of differentiating histologically between primary and metastatic growth when a complete autopsy is not available, is pointed out.

The tumor in our patient is interpreted as a dysontogenetic teratoid tumor with malignant epithelial and benign mesenchymal derivatives of multipotent embryonal cells. Clinically and histologically, the tumor in our patient resembles the embryonal carcinomas as found in the testis.

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<sup>21</sup> Gräflin, G.: Helvet. Med. acta, 8: 336, 1941.

<sup>22</sup> Fritzler, Kurt: Arch. f. klin. Chir., 19: 271, 1925.

<sup>23</sup> Foote, N. C.: N. Y. J. Med., 49: 284, 1949.

<sup>24</sup> Willis, F. A.: J. Path. & Bact., 47: 35, 1938.

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## DONOVANOSIS OF THE EPIDIDYMISS COMPLICATING TUBERCULOUS INFECTION

MILTON MARMELL, REGINA ULTMANN AND SOLOMON WEINTRAUB

*From the Department of Pathology, Harlem Hospital, Department of Hospitals,  
New York, N. Y.*

A thorough search of the literature failed to reveal any recorded cases of donovanosis (granuloma inguinale)<sup>1</sup> of the male internal genital organs. The following case of this disease, involving the epididymis, diagnosed by the demonstration of Donovan bodies in biopsy material, is deemed of sufficient interest to be reported.

Donovanosis is a chronic, specific infection manifested clinically by ulcerating granulomatous lesions involving most commonly, the skin and subcutaneous tissues. Although these manifestations are generally limited to the external genitalia and adjacent areas, the lesions may appear as primary infection, and as the result of auto-inoculation, in other parts of the body. These extragenital lesions are estimated to occur in up to 7 per cent of all cases of donovanosis.<sup>2, 3</sup> Though predominantly a cutaneous and subcutaneous disease, donovanosis may, however, involve other tissues and organs, such as the internal genital organs (reported thus far in the female only)<sup>4</sup> and may become disseminated and affect the viscera and the bones.<sup>5, 6</sup>

Histologically, the disease is characterized by the presence of cytoplasmic inclusions, the Donovan bodies, within large mononuclear cells. These bodies were described by Donovan in 1905,<sup>7</sup> and since that time are considered as pathognomonic of this infection. In 1943, Anderson<sup>8</sup> succeeded in cultivating the Donovan body in the yolk sac of the embryonated hen's egg. She and her associates characterized the organism as a gram negative bacillus, and named it *Donovania granulomatis*.<sup>9</sup> Anderson's work has been confirmed in a number of laboratories. However, experimental inoculation of these cultured organisms into man or the lower animals, does not produce the disease.<sup>10</sup>

The antibiotics have replaced the antimony compounds in the treatment of

Accepted for publication July 17, 1952.

<sup>1</sup> Marmell, M. and Santora, E.: *Am. J. Syph. Gonorr. and Ven. Dis.*, **34**: 83-90, 1950.

<sup>2</sup> Fox, H.: *J.A.M.A.*, **87**: 1785-1790, 1926.

<sup>3</sup> Chen, C. H., Greenblatt, R. B. and Dienst, R. B.: *Arch. Derm. & Syph.*, **58**: 703-715, 1948.

<sup>4</sup> Marmell, M., Fielding, W. L. and Weintraub, S.: *Am. J. Obst. & Gynec.*, **63**: 893-896, 1952.

<sup>5</sup> Lyford, J. III., Johnson, R. W., Blackman, S. and Scott, R. B.: *Bull. Johns Hopkins Hosp.*, **79**: 349-357, 1946.

<sup>6</sup> Lipp, R. G. and Bibby, D. E.: *Western J. Surg. Obst. & Gynec.*, **58**: 173-177, 1950.

<sup>7</sup> Donovan, C.: *Indian Med. Gaz.*, **40**: 411, 1905.

<sup>8</sup> Anderson, K.: *Science*, **97**: 560-561, 1943.

<sup>9</sup> Anderson, K., De Monbreun, W. A. and Goodpasture, E. W.: *J. Exper. Med.*, **81**: 25-40, 1945.

<sup>10</sup> Dienst, R. B., Chen, C. H. and Greenblatt, R. B.: *Am. J. Syph. Gonorr. & Ven. Dis.*, **39**: 152-157, 1949.

donovanosis. The effectiveness of the various antibiotics<sup>11, 12, 13, 14</sup> is bringing about a rapid disappearance of the disease in localities where it was formerly widespread.<sup>13, 15, 16</sup> With such excellent therapeutic results, a marked reduction of cases of donovanosis, if not the eradication of the disease, depends upon early diagnosis and prompt and thorough treatment.

Diagnosis depends upon the demonstration of *Donovania granulomatis* in tissue smears or in sections of biopsy material. No other criteria, clinical, therapeutic, skin tests, etc., can conclusively diagnose the disease. The organism is best demonstrated with Giemsa or Wright stains. We have found the hematoxylin and eosin stains unsatisfactory.

#### CASE REPORT

On December 12, 1950, H. H., a 39 year old man, was referred to the laboratory for a dark field examination of a penile lesion of 5 months' duration. The lesion had appeared 2 days following coitus. Self medication brought no relief. A month after the appearance of the penile ulcer, the patient noticed enlargement of the scrotum and sought medical advice. Treatment with "sulfa" drugs and penicillin, from August to December, by various physicians, had no effect upon the lesion or the scrotal swelling.

The past history was significant only in that he had had gonorrhea in 1939 and chancroid in 1940. There was no history of trauma.

Physical examination on admission revealed a thin, well developed man in moderate discomfort occasioned by the enlarged scrotum and penile ulcer. The temperature was 101F. Both testes were felt to be enlarged, the left one markedly so. There was tenderness on pressure. The left testis was irregular in outline and firm in consistency. The lesion on the penis was a shallow ulcer with well demarcated edges. It was not painful and bled easily upon touch. It was 0.5 cm. wide, involved the corona and sulcus, and extended halfway around the circumference of the penis. The penis was swollen and edematous. There were no other abnormal findings.

Dark field examination of the penile lesion was negative for *Treponema pallidum*, but the serologic tests for syphilis were strongly positive as were the Frei and Ito-Reenstierna skin tests for lymphopathia venereum and chancroid, respectively. No *Hemophilus ducreyi* or *Neisseria gonorrhoeae* were seen on smear. Tissue scrapings from the penile ulcer, stained with Giemsa, were positive for intracellular, encapsulated *Donovania granulomatis*.

A chest x-ray taken during the patient's stay in the hospital revealed small,

<sup>11</sup> Greenblatt, R. B., Dienst, R. B., Kuperman, H. S. and Reinstein, C. R.: *J. Ven. Dis. Info.*, 28: 183-189, 1947.

<sup>12</sup> Wright, L. T., Sanders, M., Logan, M. A., Prigot, A. and Hill, L. M.: *Ann. N. Y. Acad. Sci.*, 51: 318-330, 1948.

<sup>13</sup> Greenblatt, R. B., Wammock, V. S., Dienst, R. B. and West, R. M.: *Am. J. Obst. & Gynec.*, 59: 1129-1133, 1950.

<sup>14</sup> Whitaker, J. C., Wright, L. T., Beinfeld, M. S., Wilkinson, R. S. and Marmell, M.: *Antibiotics & Chemotherapy*, 1: 208-210, 1951.

<sup>15</sup> Thomas, W. L.: *Am. J. Obst. & Gynec.*, 61: 790-798, 1951.

<sup>16</sup> Hester, L. L., Jr.: Personal communication, 1952.

nodular deposits at the lung apices which were suggestive of healed tuberculous lesions. Sputum examinations (6 concentrated specimens) were negative for acid fast bacilli.

Terramycin was administered from December 6, 1950 to January 5, 1951 for a total of 23 gm. Under the influence of this treatment, the lesion healed and the temperature became normal. There was no effect upon the scrotal swelling.

On January 8, 1951, a biopsy of the epididymis was performed. Sections of the organ showed replacement of a large part of the tissue by tuberculous granulation tissue with caseation. There were occasional tubular structures which were lined by one or more cuboidal to cylindrical cells with partly indistinct, ciliated borders. The cytoplasm was clear in some instances, and granular in others. The nuclei varied somewhat in size and position. These tubular structures were

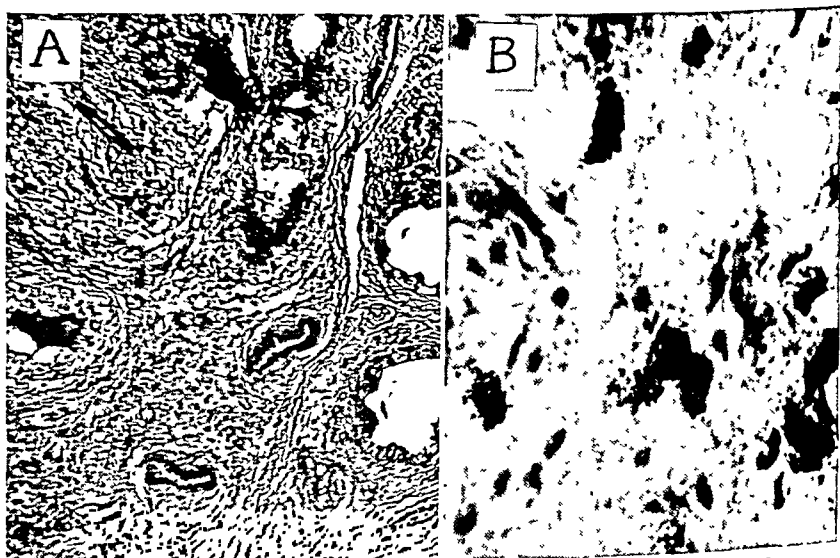


FIG. 1 *A*, epididymis showing Langhans' cells. Small, dark staining bodies are cells containing *D. granulomatis* (see *B*). Giemsa stain,  $\times 60$ . *B*, epididymis showing intracellular and extracellular Donovan bodies. Giemsa stain,  $\times 450$ .

separated by a loose, vascularized granulation tissue containing a number of mononuclear cells which, in Giemsa preparations, were seen to be laden with pink staining intracytoplasmic Donovan bodies (fig. 1). Smears and cultures of the tissue were negative for acid fast organisms.

Treatment with streptomycin was instituted (0.5 gm., b.i.d.), and on January 29, the patient was discharged "as improved." He was referred to the clinic for continuation of therapy.

The patient failed to report to the clinic, but was re-admitted to the hospital on March 22, 1951 with meningeal symptoms. He had become ill a week previous to this admission, following a "drinking spree," and had been confined to bed during that period.

When first seen on this admission, the patient appeared chronically and acutely ill. He was lethargic, but was rational as to time and place. The lungs, as on his

previous admission, were clear to auscultation and percussion. The heart was normal. A positive Kernig was elicited.

Spinal taps performed on March 22 and March 29 showed the following:

| DATE    | CELL COUNT | TOTAL PROTEIN | SUGAR    | CHLORIDES | WASSERMAN | COLLOIDAL GOLD |
|---------|------------|---------------|----------|-----------|-----------|----------------|
| 3 22 51 | 200 monos. | 228 mg. %     | 25 mg. % | 700 mg. % |           |                |
| 3 29 51 | 760 monos. | 224 mg. %     | 36 mg. % | 664 mg. % | Negative  | 1111223311     |

The patient ran a downward course throughout his 9 day hospital stay. On March 29, there was evidence of a left hemiplegia, and on March 31, the patient expired. Consent for autopsy was not obtained.

#### DISCUSSION

The purpose of presenting this case is to record the fact that the Donovan body may invade the internal genitals of the male. The lack of an autopsy makes discussion of the pathological changes produced by this organism impossible.

The most probable cause of the meningitis may have been the tubercle bacillus. We are at a loss to account for the part played by syphilis and lymphopathia venereum upon the central nervous system of our patient. There is also the report of Thierfelder and Thierfelder-Thillot,<sup>17</sup> in which donovanosis caused a paralysis in 3 of their patients.

With the demonstration of *Donovania granulomatis* in the spleen,<sup>5</sup> liver,<sup>5, 17</sup> ovaries and tubes,<sup>4</sup> bone marrow,<sup>5</sup> bladder,<sup>15</sup> bony structures,<sup>6</sup> and in this case, the epididymis, donovanosis can no longer be thought of as a cutaneous disease, but should be regarded as a systemic infection with lesions of the skin as a prominent, and perhaps, early recognizable symptom. This view has been expressed previously.<sup>19</sup> It is strengthened by the demonstration by Lyford, Scott and Johnson,<sup>19, 21</sup> that donovanosis can cause arthritis, and by the report of Thierfelder and Thierfelder-Thillot,<sup>17</sup> just referred to, that donovanosis may present symptoms referable to the central nervous system. The possible invasion of the internal organs by *D. granulomatis* must, therefore, be suspected whenever patients with cutaneous donovanosis present symptoms and complaints referable to other parts of the body. Verification of this suspicion may be difficult, and at times, impossible. This is particularly so in patients in whom the symptoms involve organs inaccessible to biopsy. In such cases, the diagnosis may be inferred from the presence of cutaneous donovanosis, and the exclusion of other possible diagnoses. Where biopsy is possible, the diagnosis may definitely be established upon the demonstration of the organism in Giemsa or Wright stained sections of the biopsied specimen.

<sup>17</sup> Thierfelder, M. V. and Thierfelder-Thillot, M.: *Arch. f. Schiffs- u. Tropen-Hyg.* 28: 221-235, 1924.

<sup>18</sup> Rhinehard, W. J. and Bauer, J. T.: *Am. J. Roentgenol. & Radium Therapy.* 57: 562-567, 1947.

<sup>19</sup> Lyford, J. III., Scott, R. B. and Johnson, R. W.: *Am. Syph. Gonorr. & Ven. Dis.*, 28: 558-610, 1944.

<sup>20</sup> Scott, R. B., Lyford, J. III. and Johnson, R. W.: *Bull. Johns Hopkins Hosp.*, 74: 213-217, 1944.



The diagnosis in the present case was complicated by the tuberculous infection. From the hematoxylin and eosin stain, the double infection was not apparent and would have been missed if Giemsa stained preparation had not been made. Tuberculosis and donovanosis do not, of course, exclude each other, and cases of cutaneous donovanosis in tuberculous patients have been reported.<sup>21, 22</sup> In view of the apparent low virulence of *D. granulomatis*,<sup>3, 10</sup> it may be said that the tuberculous infection predisposed the tissue for invasion by this organism.

#### SUMMARY

In a patient exhibiting cutaneous donovanosis, *Donovania granulomatis* was also demonstrated in the epididymis. Dissemination of this organism into the internal organs should be considered in all patients with cutaneous donovanosis who show systemic symptoms.

We are indebted to Dr. Louis T. Wright, Director of the Department of Surgery, for permission to use the case records. We wish to thank Mr. Clement A. Constan for his unstinted efforts in preparation of the photomicrographs, and Mrs. Esther Sax and Miss Anna Frankel for their co-operation in preparing the histologic slides.

<sup>21</sup> Kuhn: *Charite-Annalen*, **30**: 427-436, 1906.

<sup>22</sup> Greenblatt, R. B., Dienst, R. B., Pund, E. R. and Torpin, R.: *J.A.M.A.*, **113**: 1109-1116, 1939.

## MÜLLERIAN DUCT REMNANTS IN THE MALE

VINCENT MOORE AND GERALD E. HOWE

Congenital anomalies of the genito-urinary tract are among the most confusing problems facing the general practitioner and urologist. The developmental progressions and regressions in the genito-urinary system may distort only a minute part or may destroy the patient. Comprehension of genito-urinary embryology usually insures correction of anomalies. Misdiagnosis or misunderstanding leads to improper or disastrous surgical intervention. A paucity of reported cases may be a reflection on urologic diagnostic acumen.

The misunderstanding originates in cursory student instruction. Initial presentation in premedical work or early medical curriculum by excellent scientists untrained in clinical concepts, contributes greatly. Later, failure by clinicians to correlate pathophysiologic symptoms with embryologic deviations deepens the deficiency.

The frequent urinary anomalies are widely appreciated while genital malformations leading to distention, destruction and disaster may be overlooked. The misunderstanding of the logical clinical course of genital deviations can be obviated by discussion and publication of experience.

This paper will discuss three patients presenting disease secondary to persistent müllerian duct remnants. Pertinent embryologic concepts, diagnostic and therapeutic methods are included.

### REVIEW OF THE LITERATURE

More than forty-five articles in the English and foreign literature pertaining to müllerian duct remnants have been reviewed. Since Englisch, in 1873, reported the first cystic müllerian duct remnants at autopsy, there have been some thirty cases published. The early literature includes cases which modern roentgenological and surgical standards exclude. They were simple cysts of the prostate or seminal vesicles. Twelve cases have been proven since 1939, attesting to increased diagnostic awareness. Five of these were amenable to difficult surgical excision. Three were diagnosed by transurethral catheterization of the cyst through the verumontanum, and three by needle injection of the cystic mass. All 12 cases were palpable, eight suprapubically and four rectally. Seven had suprapubic surgery and two had combined abdominoperineal excision. Three were catheterized transurethrally with permanent evacuation.

### EMBRYOLOGY

Figure 1 illustrates the fundamental genito-urinary embryology. The fetus of ten to fourteen weeks has well developed male and female genital tubes. Ultimate sex determination causes one to go on to full development. In the female, the müllerian ducts become the tubes, uterus and cervix. In the male, only the cranial end persists as the appendix testis, while the caudal portions fuse to form the prostatic utricle.

Accepted for publication July 4, 1952.

Robert Moore, in 1937, presented a precise embryological study of 678 prostates. He proved in all the presence of an atrophic müllerian cord traversing the prostate and terminating near the verumontanum. Involution of the columnar epithelium of this tube occurred during the fourth decade. Subsequent prostatic hypertrophy did not affect the müllerian remnant. It is because of the intimate relationship to the prostate, vasa deferentia, bladder neck, seminal vesicles and rectum, that diagnosis of a dilated müllerian duct remnant is difficult and surgical removal demands careful planning and expert execution.

The müllerian duct remnant may persist in all or in part, as a tube, as a cyst, or possibly form a solid tumor. Its developmental relationships may cause its appearance at any point in the retroperitoneum, perineum or inguinal area. Depending on the presenting area, the tumor may simulate a mass of any organ or produce symptoms secondary to interference with function of the neighboring structures. Incision of fluctuant inguinal masses may cause urinary fistulas

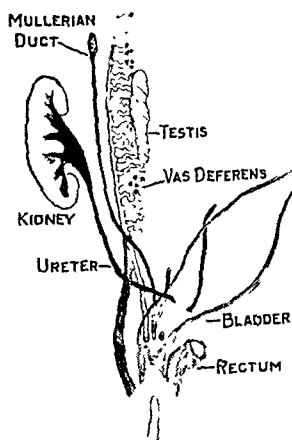


FIG. 1. Schematic diagram of primary embryological structures of genito-urinary system.

through connection of the müllerian remnant to the bladder via the prostatic utricle. Case records below illustrate perineal, abdominal and urinary manifestations.

#### DIAGNOSIS

Necessary diagnostic steps include history and physical examination, plain film of the abdomen, cysto-urethrography, excretory urography, cystoscopy, retrograde pyelography, seminal vesiculography, aspiration and injection of the cyst, retrorectal air injection, sigmoidoscopy, barium enema, laboratory examination.

The history of mild, progressive, vesical neck obstruction of short duration ending in acute retention may be helpful. Most of the patients are in their third and fourth decades although patients ranging from 21½ to 75 years of age are now known. Progressive abdominal distention with constipation or without specific symptoms suggests müllerian duct remnant tumor. Fertility and sexual potentia are unimpaired. Hematuria and infection are seldom noted.

Physical examination may show a cystic mass in the inguinal, perineal, suprapubic or retroperitoneal space. Exact location is proven by careful urological examination. Plain films of the abdomen may reveal soft tissue shadows. Cystourethrography shows the bladder neck distortion. Excretory urography indicates displacement of the kidneys, ureters and bladder and selective renal function. Cystoscopy and retrograde pyelography, performed under spinal anesthesia, visualize the verumontanum and bladder neck. Catheterization of an orifice on the verumontanum, other than the ejaculatory duct orifices, may permit injection of the duct leading to the cyst. Ejaculatory duct catheterization or bilateral seminal vesiculograms through scrotal incisions will outline the vasa deferentia and rule out dilated seminal vesicles.

Aspiration of the cyst suprapubically or perineally with injection of contrast medium permits accurate x-ray visualization. This deflation of the cyst, inciden-



FIG. 2 Case 1. A, cysto-urethrogram showing distortion and displacement of vesical neck and urethra in perineal retroprostatic cyst. B, injected perineal cyst.

tally, will relieve symptoms. Retrorectal air instillation, barium enema studies and sigmoidoscopy will give additional information.

Laboratory examination of the characteristically chocolate brown colored fluid shows no spermatozoa, parasites, or malignant cells. General biochemical studies may reveal nitrogen retention.

#### CASE REPORTS

*Case 1.* C. F. (No. 196590) a white man aged 75 years, was well until 6 months prior to admission when he suffered a perineal blow from a saddle horn. Subsequently, progressive urinary and bowel difficulty led to complete urinary retention and the necessity for liquefaction of stool to correct obstipation.

Physical examination revealed a well nourished man, distressed by a distended bladder. A tender, round, cystic mass, 10 cm. in diameter, was found displacing the rectum to the right and obscuring the prostate (fig. 2, A). Under anesthesia, the prostate was found displaced anteriorly, upward and to the right. Cystourethroscopy and retrograde pyelograms were normal except for distortion of the

bladder neck. The cyst could not be catheterized transurethrally. Seminal vesiculography was normal. Aspiration of 150 cc chocolate fluid and injection of radio-opaque material demonstrated the relationships to pelvic structures (fig. 2, *B*). With the cyst empty, the prostate and seminal vesicles were found in normal position. All obstructive rectal and urinary symptoms were relieved by aspiration. Sigmoidoscopy revealed normal rectal mucosa. The cyst refilled in 5 days.

Through a perineal incision, the cyst was excised. Firm adherence to the caudal rectal wall prevented complete separation. A portion of the cyst wall 1 by 2 cm. was left in situ. Separation from the prostate and seminal vesicles was simple and complete. Firm wound closure with Penrose drainage resulted in a cleanly healed incision in 9 days. All preoperative symptoms had been relieved without sacrifice of urinary or rectal control. Histological study of the specimen revealed a papillary cystadenoma of ovarian type. Clinical observation for 18 months found the patient in good health without symptoms but presenting a 2 by 3 cm. irregular, fibrous mass of unchanging character anterior to the rectum. Residual urine of 300 cc developed 21 months after surgery. Perineal biopsy of a now suspiciously hard prostate showed adenocarcinoma of the prostate. Transurethral resection of the prostate and the bladder neck extension was followed by orchiectomy and stilbesterol therapy.

*Case 2.* A. W. (No. 186589), a 58 year old white man was first seen with obstructive urinary symptoms of 3 months' duration. Three years previously he had noted the painless, asymptomatic development of a right lower quadrant mass. Physical examination showed a huge, cystic mass filling the entire right half and left upper quadrant of the abdomen. It was movable, irregular, non-tender and shifted with respiration. Rectally, the grade 1 enlarged, benign prostate was displaced to the left. Rectal palpation of the mass showed no definite prostatic connection.

Urethrography showed the urethra displaced to the left. Excretory urography indicated prompt function of a mildly dilated left kidney (fig. 3, *A*). No renal function or outline was seen on the right. Cystoscopy revealed absence of the right ureteral orifice and trigonal wing. Urethroscopy revealed a normal veru but ejaculatory ducts and anomalous orifices could not be catheterized. A normal left seminal vesiculogram was made but no right vas could be found. Transabdominal aspiration of the cyst yielded 5000 cc chocolate fluid, free of spermatozoa, parasites and malignant cells. Injection of radio-opaque fluid visualized the described extended abdominal position (fig. 3, *B*). Evacuation of the cyst relieved all symptoms, and at his demand, the patient was discharged. Recurrence of the mass 47 days later led to transperitoneal and retroperitoneal removal. No right kidney or right ureter was present. The caudal pole ended in the retro-trigonal area but was detached easily without injury to the bladder or urethra. Recovery was prompt and complete without sacrifice of urinary or rectal control. Histological study showed only collagenous walls without epithelium.

*Case 3.* Y. L. (No. O-5680A). A Chinese man, now 26 years old, at age of 12

years suffered severe urinary tract infection. At 18 years, albuminuria caused military rejection. Three years later he suffered several episodes of gross total hematuria. At 23 years, a flat film of the abdomen, made for epigastric complaints, revealed calcium opacities in the urinary bladder area although he had no urinary



FIG 3 Case 2 *A*, excretory urogram showing prompt function of left kidney over shadowed by large abdominal mass. *B*, radio-opaque injection of cystic abdominal mass



FIG 4 Case 3 *A*, calcium opacities in true pelvis. *B*, cystogram showing suspicious right ureteral reflux

complaints. At 25 years, perineal tightness and discomfort developed. General and urologic physical examination was normal.

Calcium opacities in the true pelvic area were again present on the plain film (fig. 4, *A*). Cystograms suggested a right ureteral reflux (fig. 4, *B*). Excretory

urography showed a normal left kidney and ureter but no sign of pelvis or renal outline on the right. Cysto-urethroscopy showed papillary degeneration of the verumontanum with two slit-like ostia near the trigonal apex. No right trigonal wing or ureteral orifice was present. When catheters were inserted into these aberrant ostia, both entered a common dilated, retrovesical tube whose upper end extended retroperitoneally to the right renal fossa (fig. 5). A left seminal vesiculogram was normal but scrotal exploration revealed no right vas.



FIG. 5. Case 3. Retrograde filling of patent right mullerian duct



FIG. 6. Case 3. Calcium densities in persistent left mullerian duct remnant

Exploration of the right renal fossa through a flank incision revealed no renal tissue. The cranial two-thirds of the duct was dissected to the pelvic brim. Through a lower right paramedian rectus incision, dissection of the mullerian remnant was completed to its caudal end. Inflammatory and fibrous fixation prevented clean separation from the trigone. The wall was trimmed from the bladder and the vesical opening closed. In the operating room, combined rectal and pelvic palpation and x-rays revealed persistent calculi to the left of the midline (fig. 6). It was deemed wise to terminate the operative procedure.

The postoperative course was turbulent. He recovered completely but pyuria persisted. Cystoscopy revealed destruction of the vesical repair and a small epithelial-lined diverticulum. No source of pyuria was found. It is the authors' opinion that the left müllerian duct remnant contains the remaining calculi and that diligent observation will visualize its ostium in the posterior urethra. This is the source of the persistent pyuria.

#### DISCUSSION

The first case illustrates a cystic müllerian duct remnant with no deformity of the upper and complete obstruction of the lower urinary tract and rectum. The extraprostatic mass was easily excised with excellent results. The papillary degeneration was of interest. The usual pathological change is that of a collagenous tube or cyst with or without epithelium varying from columnar to transitional and low grade inflammatory changes. Papillary cystadenoma of ovarian type was reported first.

The subsequent proven carcinoma of the prostate in the first patient raised the question of adenocarcinoma of the prostate being present in the completely extraprostatic müllerian duct remnant cyst. Study of microscopic sections of both specimens by a number of pathologists has not positively answered this question.

The second and third patients showed congenital absence of the right side of the genito-urinary system. Neither patient had any right vas deferens, right trigonal wing, right ureteral orifice, right ureter or right kidney. The entire metanephric development was absent. Instead, a dilated müllerian duct remained. The duct of the second patient ended in a cul-de-sac under the trigone and posterior urethra. Although closely contiguous, it was easily separated and no clear connection was demonstrated. The third patient had an even greater congenital defect in that both müllerian ducts persisted. The right was excised. The caudal stump of the left müllerian duct is still present as evidenced by stones posterior to the bladder and outside the seminal vesicles, and persistent pyuria with no other source. The ostium of the left müllerian duct must enter the posterior urethra and will be found sooner or later. Thus is demonstrated the importance of considering müllerian duct remnants when there is an aberrant ureteral orifice or seeming agenesis of the trigonal wing, ureter or kidney.

The perineal cyst is the second müllerian duct remnant to be reported containing a papillary tumor. The second patient presented the largest such cyst on record; it contained 5000 cc of chocolate fluid. The three stones, measuring 1 by 1½ cm. each, in the duct of the third patient are the largest such concretions in the literature of these cysts.

#### SUMMARY

The cases of 3 patients with dilated müllerian duct remnants have been presented. With a knowledge of the embryology of the genito-urinary tract and an awareness of the possible existence of such defects, it was possible, by careful



examination and the use of the precise urological methods described, to make an accurate diagnosis. This, in turn, allowed prompt surgical treatment and cure. More widespread discussion of müllerian duct remnants, their symptoms and signs, will lead to increased recognition and proper treatment.

## A FIVE YEAR SURVEY OF TRAUMATIC UROGENITAL EMERGENCIES

GEZA SCHINAGEL AND GEORGE SEWELL

*From the Wayne University College of Medicine and City of Detroit Receiving Hospital,  
Detroit, Mich.*

The purpose of this paper is a statistical presentation of the traumatic urogenital emergencies which have been admitted, during a 5 year period, from January 1, 1947 to December 31, 1951, to the Receiving Hospital of the City of Detroit.

During these 5 years, there have been a total of 88,171 admissions to the hospital of which patients 9,801 or 11 per cent had some medical or surgical urogenital disease. Of these 9,801 patients, 346 or 3.6 per cent were traumatic urogenital emergencies, making them about 0.4 per cent of the total hospital admissions. The seriousness of the injuries, of this group, necessitated their admission to the hospital, otherwise they would have been handled as ambulant patients through the out patient department. These latter have not been included in these statistics.

The purpose of this paper is not to elaborate on the various methods of handling trauma of the urogenital tract, but there has been an effort to treat these emergencies immediately and as far as possible to do so in one complete operation, insofar as conditions permit. The basic principles of their treatment have been as follows: Relief of shock, with adequate blood replacement; recognition and repair of all injuries to various systems involved; extensive urinary drainage, often with diversion of the urinary stream for the time necessary, with co-operation, at once, from the various surgical specialties involved.

The advantages of the co-operation of teams from the various surgical specialties are at once apparent. These patients have all been admitted to the general surgery service first and immediately the other surgical specialties are called for diagnostic procedures and surgical assistance. The following statistics (tables 1, 2, 3, 4, 5, 6) based on these 346 cases of urogenital emergencies, are submitted for evaluation.

We note that traumatic urogenital emergencies are more prevalent between the age of 41-70 years in the white male, and between 21-50 in the colored males. In this age group, on the average, there are already many urogenital pathological changes. We may conclude, therefore, that they might be more vulnerable to any trauma to which they might be afflicted.

We find that car accidents have been the cause in 31.7 per cent, directly inflicted traumas in 35 per cent, and accidentally falling down in 26 per cent. There have been 51 persons (14.5 per cent) intoxicated, in car accidents 13 persons (12 per cent). We may assume then that alcoholism was not a main contributory cause to these injuries.

As in 39.4 per cent of the traumatic urogenital emergencies, bone fractures have

TABLE 1. *Number of hospital admissions*

| YEAR            | TOTAL<br>ADMISSIONS<br>TO HOSPITAL | PATIENTS WITH UROGENITAL<br>MEDICAL OR SURGICAL<br>DISEASE |          | THOSE WITH UROGENITAL<br>TRAUMATIC EMERGENCIES |                         | % OF TOTAL<br>ADMISSIONS |
|-----------------|------------------------------------|------------------------------------------------------------|----------|------------------------------------------------|-------------------------|--------------------------|
|                 |                                    | Number                                                     | Per cent | Number                                         | Per cent<br>pathologies |                          |
| 1947            | 17,750                             | 2,012                                                      | 11.3     | 85                                             | 4.22                    | 0.5                      |
| 1948            | 17,275                             | 2,095                                                      | 12.1     | 80                                             | 3.09                    | 0.5                      |
| 1949            | 17,093                             | 1,682                                                      | 9.8      | 64                                             | 3.8                     | 0.4                      |
| 1950            | 18,152                             | 2,121                                                      | 11.7     | 76                                             | 3.58                    | 0.4                      |
| 1951            | 17,901                             | 1,891                                                      | 10.6     | 41                                             | 2.16                    | 0.2                      |
| Total . . . . . | 88,171                             | 9,801                                                      | 11.1     | 346                                            | 3.53                    | 0.4                      |

TABLE 2. *Age and sex of patients with traumatic urogenital injuries*

| AGE                  | MALE  |         | FEMALE |         |
|----------------------|-------|---------|--------|---------|
|                      | White | Colored | White  | Colored |
| 4 months to 10 years | 10    | 6       | 2      | —       |
| 11-20 years          | 10    | 16      | 3      | —       |
| 21-30 years          | 18    | 36      | 9      | 7       |
| 31-40 years          | 10    | 31      | 5      | 9       |
| 41-50 years          | 23    | 17      | 6      | 6       |
| 51-60 years          | 26    | 10      | 5      | 3       |
| 61-70 years          | 38    | 5       | 7      | 3       |
| 71-80 years          | 15    | —       | 4      | —       |
| 81-89 years          | 5     | —       | 1      | —       |
| Summary              | 155   | 121     | 42     | 28      |
| Per cent . .         | 44.8  | 35.1    | 12.1   | 8       |
|                      | 80    |         | 20     |         |

TABLE 3. *Causes of urogenital injuries*

|                   | TOTAL | PER CENT |
|-------------------|-------|----------|
| Car accidents     | 110   | 31.7     |
| Falls             | 90    | 26       |
| Assaults          | 49    | 14       |
| Gunshot wounds    | 43    | 12       |
| Stabbings         | 28    | 8.9      |
| Burns             | 13    | 3.7      |
| Suicidal attempts | 13    | 3.7      |

been present, the teamwork of the orthopedic surgeon with the urogenital surgeon is important.

Table 5 shows that the most frequent emergencies, on account of traumatic injuries, have been those of the external genitalia, os penis and scrotum and its

contents. Afterwards came, in decreasing numbers, the injuries of the kidneys, bladder, prostate, urethra and the ureters.

The prostate was traumatized in 38 cases. We believe that the prostate may, as a result of adjacent or direct trauma, become edematous and hyperemic. Consequently, we believe that some of the urinary retention, following a traumatic urogenital injury, may not be due, solely, to direct injury with blood clots in the bladder, etc., but often are due to an already slightly enlarged and traumatized prostate with its accompanying edema and hyperemia.

TABLE 4. *Symptoms and fracture complications, other than shock or pain*

|                        | TOTAL | PER CENT |
|------------------------|-------|----------|
| Hematuria              | 131   | 37.8     |
| Urinary retention      | 41    | 11.8     |
| Pelvic fractures       | 43    | 12.4     |
| Femur (neck) fractures | 21    | 6        |
| Multiple fractures     | 73    | 21       |

TABLE 5. *Survey according to individual organs affected*

| ORGANS           | ADMISSIONS       |                      | TRAUMATIC INJURIES |                      | AVERAGE<br>% YEARLY |     |
|------------------|------------------|----------------------|--------------------|----------------------|---------------------|-----|
|                  | 5 Year<br>period | Per cent<br>of total | 5 year<br>period   | Per cent<br>of total |                     |     |
| Kidney           | 2,411            | 24.5                 | 99                 | 4.1                  | 20                  | 4.6 |
| Ureter           | 956              | 9.7                  | 22                 | 2.3                  | 4.4                 | 2.6 |
| Bladder          | 1,874            | 19.1                 | 74                 | 3.9                  | 15                  | 4.5 |
| Urethra          | 1,168            | 11.9                 | 33                 | 2.8                  | 6.6                 | 2.9 |
| Testis           | 284              | 2.8                  | 11                 | 4.5                  | 3.5                 | 5.7 |
| Epididymis       | 294              | 2.9                  | 9                  | 3                    | 2                   | 3   |
| Tunica vaginalis | 125              | 1.2                  | 6                  | 4.8                  | 1.2                 | 2.3 |
| Scrotum          | 128              | 1.3                  | 27                 | 2.1                  | 5.4                 | 9.9 |
| Vas deferens     | 225              | 2.3                  | —                  | —                    | —                   | —   |
| Spermatic cord   | 60               | 0.6                  | 3                  | 5                    | 0.4                 | 2.4 |
| Seminal vesicles | 35               | 0.4                  | —                  | —                    | —                   | —   |
| Prostate         | 1,700            | 17.4                 | 38                 | 2.2                  | 7.4                 | 2   |
| Penis            | 541              | 5.5                  | 24                 | 4.4                  | 5.                  | 4.5 |

#### COMMENT

We must always bear in mind, that in traumatic urogenital injuries, the urogenital damages are only a part of the clinical picture, often a small part of the whole problem. In the majority of cases, other types of injuries are present such as multiple fractures, injuries of the liver, spleen, intestines, adynamic ileus, subdural hematomas and cerebral concussions, etc., etc.

It is a known fact that 5 to 7 per cent of urogenital injuries should be expected in abdominal injuries; and in thoraco-abdominal injuries, 10 per cent of them should be expected. Consequently, in any case, when there is a suspicion of combined injuries, exploration with a combined surgical team is indicated.

TABLE 6. *Urogenital injuries and operative mortality*

## 1. Kidney: 99 cases; 11 died (or 11 per cent)

|                       |          |        |               |
|-----------------------|----------|--------|---------------|
| a) Contusions         | 71 cases | 4 died | 5.6 per cent  |
| b) Ruptures           | 28 cases | 7 died | 25 per cent   |
| c) Surgically treated | 28 cases | 5 died | 17.8 per cent |
| (Repair)              | 19 cases | 4      | 21 per cent)  |
| (Nephrectomy)         | 9 cases  | 1      | 11 per cent)  |

The fatalities were the following:

| NUMBER<br>INITIALS  | AGE, RACE, SEX     | CAUSE OF INJURY               | FINDINGS AND OPERATION                                                              |                                                                                              | DIED        |
|---------------------|--------------------|-------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|-------------|
|                     |                    |                               | Surgical                                                                            | Urogenital                                                                                   |             |
| 47: 17,167<br>H. M. | 25, white,<br>male | Gunshot                       | Transverse colon<br>perforation;<br>left hemato-<br>thorax                          | Cortical rupture,<br>right kidney;<br>retroperitoneal<br>hematoma;<br>kidney suture          | Days<br>1st |
| 47: 11,492<br>F. J. | 23, Negro,<br>male | Gunshot, left<br>axillar line | Fracture, left<br>9th rib, splen-<br>ectomy; colos-<br>tomy                         | Craterlike defect<br>in left kidney;<br>retroperitoneal<br>hematoma;<br>nephrectomy,<br>left | 5th         |
| 49: 6,173<br>J. K.  | 30 Negro,<br>male  | Shot by wife                  | 8 ileum perfora-<br>tions; dia-<br>phragmatic<br>hernia                             | Laceration, lower<br>pole, left kid-<br>ney; kidney<br>suture                                | 1st         |
| 50: 4,140<br>F. W.  | 35, Negro,<br>male | Gunshot                       | Perforation liver<br>and left femo-<br>ral artery                                   | Perforation, right<br>kidney; kidney<br>suture                                               | 4th         |
| 51: 8,886           | 39, Negro,<br>male | Beaten up                     | Fracture of left<br>10th rib; splen-<br>ectomy; resec-<br>tion of 35 cm.<br>jejunum | Laceration, su-<br>perior pole,<br>left; kidney<br>suture                                    | 4th         |

## 2. Ureter: 22 cases; 1 died (or 4.5 per cent)

|                     |                    |         |                                                             |                                                              |     |
|---------------------|--------------------|---------|-------------------------------------------------------------|--------------------------------------------------------------|-----|
| 50: 11,765<br>A. M. | 44, Negro,<br>male | Gunshot | Perforation sup.<br>mesenteric ves-<br>sels; cecum<br>wound | Laceration right<br>ureter; retro-<br>peritoneal<br>hematoma | 1st |
|---------------------|--------------------|---------|-------------------------------------------------------------|--------------------------------------------------------------|-----|

## 3. Bladder: 74 cases

- |                |          |         |                 |
|----------------|----------|---------|-----------------|
| a) Rupture     | 20 cases |         |                 |
| b) Perforation | 10 cases | 13 died | (43 per cent)   |
| c) Contusions  | 44 cases | 19 died | (41.8 per cent) |

The bladder findings in this group were only incidental, accompanying serious injuries of other organs.

## 4. Urethra: 33 cases; 9 died. (27 per cent)

- |               |          |
|---------------|----------|
| a) Rupture    | 7 cases  |
| b) Laceration | 26 cases |

TABLE 6. *Continued*

5. Spinal injuries cord bladder: 10 cases; 2 died (20 per cent)

From the 117 patients, who comprised the groups 3, 4 and 5, cystostomy was performed 31 times with a mortality of 15 (or 12 per cent) (respectively 48.3 per cent).

Fatalities were the following:

| NUMBER<br>INITIALS   | AGE, RACE, SEX      | CAUSE OF INJURY                                        | FINDINGS AND OPERATION                                                                 |                                                                   | DIED               |
|----------------------|---------------------|--------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|--------------------|
|                      |                     |                                                        | Surgical                                                                               | Urogenital                                                        |                    |
| 47: 13,071<br>A. W.  | 45, male<br>white   | Car accident                                           | Fracture of:<br>Bilat. 7th, 12th<br>ribs; right hip.<br>tibia, fibula                  | Rupture of<br>bladder                                             | <i>Days</i><br>2nd |
| 47: 8,488<br>G. H.   | 30, white<br>male   | Hit by truck                                           | Left ascend and<br>descend pubic<br>bone fracture;<br>separation of<br>symphysis pubis | Rupture of<br>bladder                                             | 7th                |
| 48: 7,875<br>E. H.   | 16, Negro,<br>male  | 24 hours ago<br>bicycle handle<br>penetrated<br>rectum | Peritonitis; sig-<br>moid colostomy.                                                   | Rupture of<br>bladder                                             | 2nd                |
| 48: 14,550<br>R. D.  | 46, Negro,<br>male  | Shot in back                                           | Paralysis below<br>first lumbar<br>vert.; trans-<br>verse myelitis                     | Cord bladder;<br>peri-urethral,<br>scrotal, perineal<br>abscess   | 223                |
| 48: 16,138<br>T. M.  | 48, white<br>male   | Struck by car                                          | Fracture of:<br>Comp. left<br>tibia; commun.<br>pelvis                                 | Lacerated bladder                                                 | 1st                |
| 48: 140<br>I. W.     | 75, white<br>male   | Auto accident                                          | Fracture of:<br>Pelvis, multiple<br>ribs, tibia,<br>fibula                             | Rupture of<br>urethra                                             | 2nd                |
| 49: 2,927<br>M. K.   | 68, White<br>female | Struck by<br>streetcar                                 | Fracture of pel-<br>vis, left femur;<br>subdural hema-<br>toma; trephine               | Rupture of<br>bladder                                             | 5th                |
| 49: 3,982<br>S. C.   | 62, white<br>male   | Run over by<br>train                                   | Fracture of pelvis                                                                     | Laceration of<br>bladder                                          | 17th               |
| 49: 8,692<br>S. L.   | 4, white<br>female  | Hit by truck                                           | Fracture of both<br>pelvic rami;<br>left diaphrag-<br>matic hernia                     | Rupture of<br>bladder                                             | 1st                |
| 49: 9,386<br>W. P.   | 36, Negro,<br>male  | Shot                                                   | Perforation of<br>small bowels<br>and cecum, 20<br>times. Liver<br>laceration.         | Bladder perfora-<br>tion                                          | 1st                |
| 50: 17,860<br>J. CH. | 75, white<br>male   | Hit by car                                             | Fracture of right<br>tibia.                                                            | Bladder rupture;<br>urinary extra-<br>vasation; peri-<br>tonitis. | 5th                |

TABLE 6. *Continued*

| NUMBER<br>INITIALS  | AGE, RACE, SEX    | CAUSE OF INJURY                   | FINDINGS AND OPERATION                                                          |                                     | DIED               |
|---------------------|-------------------|-----------------------------------|---------------------------------------------------------------------------------|-------------------------------------|--------------------|
|                     |                   |                                   | Surgical                                                                        | Urogenital                          |                    |
| 50: 11,061<br>D. C. | 44, white<br>male | Hit by car                        | Fracture of both<br>pelvic rami<br>ulna; ruptured<br>diaphragm.,<br>thoracotomy | Rupture of blad-<br>der and urethra | <i>Days</i><br>4th |
| 50: 16,788<br>F. S. | 68, white<br>male | Auto accident                     | Skull fracture                                                                  | Rupture of dome<br>of bladder       | 1st                |
| 50: 4,979<br>R. D.  | 60, white<br>male | Fell from 3rd<br>floor; alcoholic | Fracture of:<br>Vertex; mul-<br>tiple ribs                                      | Bladder rupture                     | 3rd                |
| 51: 330<br>L. S.    | 42. Negro<br>male | Shot                              | 7 cm. jejunal re-<br>section; tho-<br>ractory                                   | Bladder perfora-<br>tion            | 1st                |

## 6. External genitalia: 51 cases; 3 died (5.8 per cent)

|                     |                    |                                           |                                                              |  |      |
|---------------------|--------------------|-------------------------------------------|--------------------------------------------------------------|--|------|
| 47: 11,200<br>S. S. | 43, Negro,<br>male | Burned                                    | 3rd degree burn<br>on penis and<br>scrotum                   |  | 4th  |
| 48: 13,295<br>J. E. | 61, white<br>male  | Car accident                              | Fracture of left<br>femur; ulcer-<br>ated, penis<br>scrotum. |  | 3rd  |
| 49: 15,307<br>L. M. | 49, Negro,<br>male | Set fire with<br>gasoline on<br>genitalia | 3rd degree burn<br>of lower ab-<br>domen, penis,<br>scrotum. |  | 20th |

As a traumatized kidney has great capacity to repair, we treated contusions of the kidneys mostly conservatively, under a watchful observation; and, yet, of the 71 patients with contusions of the kidneys, as a part picture of their other, more serious associated injuries, thirty-eight (53.5 per cent) died, clearly indicating that the cause of this sad picture was not the kidney contusion itself.

Injuries, which resulted in disrupting the continuity of the pelvic girdle in about 12.4 per cent, mostly through damages of the lower abdomen, hips, buttocks, thighs and perineum, have been usually connected with perforation or rupture of the urinary bladder. In these cases, because of masking effects of antibiotics, we must be even more suspicious of urinary extravasation and its dire consequence: perivesical and retroperitoneal cellulitis or peritonitis.

The seriousness of the associated injuries shows that the mortality rate, in the above groups, was very high. It will be noted, however, that in nearly all cases the injuries to other tracts were serious and extensive. Deaths occurred within the first 48 hours, in spite of copious blood transfusions and the usual supportive measures, in 43.1 per cent of these patients in whom some contusion of the urinary bladder wall was only incidentally diagnosed.

Perivesical, retroperitoneal and ischiorectal extravasations were found in the injuries of the membranous or prostatic urethra, whereas extravasation of the scrotum, penis, perineum and lower abdomen appeared mostly in urethral injuries below the urogenital diaphragm. In this group, the mortality rate was 27 per cent. The primary cause of the 5.8 per cent mortality rate in those with injuries of the external genitalia was the seriousness of injuries in other organs, as we treated them conservatively with hemostasis, tissue conservation and débridement. Rarely was direct surgery to these organs used.

#### SUMMARY

Three hundred and forty-six traumatic urogenital emergencies have been analyzed, from 88,171 patients admitted to the Receiving Hospital, City of Detroit, during the 5 year period from January 1, 1947 to December 31, 1951.

The urogenital postoperative mortality of 346 traumatic urogenital injuries has been 24 (6.9 per cent).

As the traumatic urogenital injuries, in most cases, show only a partial picture of the inflicted damages, in handling them teamwork of the different surgical specialties is necessary. In this group, the mortality was 54 (16.7 per cent).

It is pointed out that the clinical picture of a traumatic urogenital injury may be influenced by pre-existing urogenital disease.

The role of a traumatized prostate is emphasized in urinary retention following an injury.

Although the automobile is a large factor in the production of these traumatic urogenital injuries (31.7 per cent), it was closely followed, as a causative factor in our series, by falling down, as from a ladder or off a building, etc. (26 per cent).

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## PRELIMINARY REPORT ON THE LOWERING OF PROTHROMBIN BY GANTRISIN

SAMUEL SILBERG, CYRIL BRUNO, SOLOMON KEESAL  
AND SILVIO MICELI

*From the Department of Urology, Philadelphia General Hospital, Philadelphia, Pa.*

The drug Gantrisin has been used extensively and effectively by most urologists in treating infections of the genito-urinary tract and by men in other fields of medicine when a sulfonamide drug is indicated.

The urology department of the Philadelphia General Hospital first used this drug experimentally in 1947, and it is from this work that Haines and Miceli<sup>1</sup> reported on their encouraging results in the management of *Proteus* infections of the urinary tract. Later in 1949 McCrea and Schneeberg<sup>2</sup> reported on the effectiveness of this drug in many other infections of the genito-urinary tract. Carroll, Allen, and Flynn<sup>3</sup> noted the usefulness of Gantrisin against infections of *Proteus*, *Escherichia coli*, and *Alcaligenes*; and they advised the use of a dose of 2 gm. orally every 6 hours. They noted absence of local or systemic reactions and stated that the concentrated use of alkali and forced fluids was not necessary.

Gale<sup>4</sup> reported the presence of petechial hemorrhages with the use of Gantrisin. In his patient petechiae developed of pin point size to 1 cm. in diameter, following the use of Gantrisin for cystitis.

The prolongation of prothrombin time with patients on sulfonamide therapy was noted by Kapnick and Stewart<sup>5</sup> in 1942, when they measured the prothrombin in 68 patients who received sulfonamide therapy. They found that 21 per cent showed a significant decrease in the prothrombin level during chemotherapy. Studies carried out by Seeler, Muckett, Graessle, and Silber<sup>6</sup> showed the effect of sulfaquinoxaline on the prothrombin in rats. Determination of the prothrombin time in these animals showed that a single massive dose of sulfaquinoxaline caused a prompt and marked drop in prothrombin levels which in the majority of the rats reached a low level in about 24 hours after a single dose and was back to normal in 48 hours. They also noted that when vitamin K was given simultaneously with sulfaquinoxaline, the development of hypoprothrombinemia was prevented and if given when hypoprothrombinemia was established it would cause prompt recovery.

### CASE REPORTS

The following are 5 cases of patients with hemorrhage or hemorrhagic tendencies due to prolongation of blood prothrombin time with the etiologic agent thought to be Gantrisin.

Accepted for publication June 4, 1952.

<sup>1</sup> Haines, W. H. and Miceli, S.: *Penn. Med. J.*, 50: 1328, 1947.

<sup>2</sup> McCrea, L. E. and Schneeberg, A. A.: *J. Internat. Coll. Surg.*, 14: 721, 1950.

<sup>3</sup> Carroll, G., Allen, H. M. and Flynn, H.: *Urol. & Cutan. Rev.*, 53: 677-83, 1949.

<sup>4</sup> Gale, G. L.: *Canad. M. Ass. J.*, 64: 252-3, 1951.

<sup>5</sup> Kapnick, D., Stewart, J. D. and Lyons, C.: *New Eng. J. Med.*, 227: 944, 1942.

<sup>6</sup> Seeler, A. O., Muckett, C. W., Graessle, O. and Silver, R. H.: *J. Pharmacol. and Exper. Therap.*, 82: 357, 1944.

*Case 1.* A 69 year old white woman was admitted to the Philadelphia General Hospital on July 15, 1951 with complaint of painful urination, weakness and pain in both upper abdominal quadrants of 2 months' duration. Physical examination on admission revealed that the patient was dehydrated and lethargic. A mass was palpated in both the right and left upper quadrants. Laboratory studies: Hemoglobin 10.5 gm. per cent, white blood cells, 11,750; sugar, 114; blood urea nitrogen, 95; CO<sub>2</sub>, 29 vol. per cent; chlorides, 644; urinalysis, white blood cells, 30-35 per high power field, and protein (serum), 5.7 gm.

The patient was given parenteral fluids on admission and improved within 48 hours. On July 19, laboratory studies showed the following: blood urea nitrogen, 48; CO<sub>2</sub>, 38 vol. per cent hemoglobin, 9.6 gm. per cent; white blood cells 5,900; prothrombin, 98 per cent; ceph. flocc., 4 plus; thymol flocc.—0; thymol turbidity, 1.5; and BSP retention, 23 per cent.

A diagnosis of massive pyohydronephrosis of the right kidney with *Pseudomonas aerogenes* and *Coli aerogenes* was made. The patient was started on Gantrisin on July 29. August 10, a right nephrectomy was done, and postoperatively the patient was started on streptomycin and penicillin. The patient did well until August 20, ten days postoperative, when she started to bleed from her wound. It was thought that a vessel at the operative site had ruptured. The patient was being prepared for surgery when it was noted that she had other ecchymotic areas over her body. Within 12 hours the patient began to bleed from her nose, vagina, mouth and urethra. At this time a blood dyscrasia was suspected. The prothrombin time was less than 5 per cent of normal; platelet count, 206,000; bleeding time, 1 minute; clotting time, 9 minutes; hemoglobin 6.8 gm. per cent; blood urea nitrogen, 92 gm. The operation was canceled and all medications were discontinued at this time. Massive doses of vitamin K (75 mg. 2.4 hours) and blood transfusions were given. The prothrombin time gradually returned to normal: August 21, 22 per cent; August 22, 40 per cent; August 27, 85 per cent. The blood urea nitrogen likewise dropped to normal within 4 days. On August 27 a series of liver function tests showed the following: BSP retention, 16 per cent; ceph. flocc., 0; thymol flocc., 0; thymol turbidity, 3.6 u.; total cholesterol, 137 with 57 per cent esters. August 31, the prothrombin time was 98 per cent of normal.

This patient continued to do well and was discharged to the urology clinic for follow-up study. The patient received 108 gm. Gantrisin (1 gm. q.i.d.).

*Case 2.* A 65 year old white man was admitted to the Surgical Service of the Philadelphia General Hospital on June 29, 1951. The patient gave a 3 day history of crampy abdominal pain and constipation. Physical examination revealed tenderness and rigidity in both lower quadrants, most marked on the right side. The white blood cell count upon admission was 18,000 with 97 per cent polymorphonuclears. Blood urea nitrogen was 54 mg. A diagnosis of acute appendicitis was made and an operation performed that night. The patient was found to have a large and inflamed right kidney, with the appendix bound down with dense adhesions. Postoperatively the patient was transferred to the urological service.

On July 3, the blood urea nitrogen was 112 mg.; urinalysis showed a specific gravity of 1.009; albumin, 2 plus; pyuria and hematuria; CO<sub>2</sub>, 27 vol. per cent. A flat film of the abdomen showed nephrolithiasis of the left kidney and enlarged kidney shadows bilaterally. At this time the patient was started on Gantrisin and penicillin. The patient was also placed on catheter drainage and the blood urea nitrogen returned to normal by July 18; blood urea nitrogen, 18 mg. Excretory urography and retrograde pyelography confirmed the diagnosis of marked bilateral hydronephrosis with two large calculi in the left renal pelvis. Urine cultures revealed bilateral infection with *Pseudomonas* and *Proteus*. On July 31 a plastic repair of the left renal pelvis was done and the stones removed. A nephrostomy was performed at the same time on the left side to insure drainage. The patient did very well postoperatively with good drainage from the nephrostomy.

On August 21, the patient had gross hematuria, which was found to be coming from both the nephrostomy tube and the bladder. On August 22 the patient had a nose bleed and also profuse bleeding from small cuts sustained while shaving. Prothrombin time determined at this time was 7 per cent. Further studies at the time of bleeding showed the following: Hemoglobin 9.6 gm. per cent; total protein, 7.1 gm/100 with an A/G ratio of 4.9/2.2; bilirubin, 0; ceph. flocc., 0; thymol flocc., 0; thymol turbidity, 0.7u; and PSP retention of 4 per cent in 30 minutes. The Gantrisin was discontinued and the patient was given vitamin K (75 mg. b.i.d. for 5 days). On August 31, the prothrombin level was 49 per cent; on September 4, the prothrombin was 55 per cent. Following the discontinuation of Gantrisin the patient had no other episodes of bleeding. This patient received a total of 266 gm. of Gantrisin.

*Case 3.* A 74 year old white man was admitted with a 3 months' history of dysuria, nocturia, frequency, dribbling, and difficulty starting his stream. Admission physical revealed a well developed, well nourished elderly white man in no acute distress. Positive findings included: blood pressure 262/146; coarse rales posteriorly of both lung bases, liver palpable 3 cm. below the costal margin; prostate enlarged two times normal, stony hard in consistency, and a 3 plus pitting edema of the ankles. The diagnosis on admission was HCVD with decompensation, and carcinoma of the prostate. Laboratory studies included: blood urea nitrogen 8 mg. total protein, 6.7 gm.; CO<sub>2</sub>, 53 vol. per cent; chlorides, 574 mg.; hemoglobin 14.9 gm. per cent; white blood cells 5,800; urinalysis negative except for 10-15 red blood cells.

The patient was placed on catheter drainage and received digitalis and mercurial diuretics. On November 4, the patient was started on Gantrisin (2 gm. q.i.d.).

On November 9, the patient had a retropubic prostatectomy and withstood the procedure well. A wound infection developed and the patient was started on terramycin (500 mg. q. 6 hours for 5 days). On November 14, studies showed the following: Prothrombin time was 49 per cent; bleeding time was 1 minute and 15 seconds; clotting time, 4 minutes and 25 seconds; platelets count was reported as plentiful, and hemoglobin 12.6 gm. per cent. The patient began

showing clinical improvement, when on November 23 a hemorrhage occurred from the nose and mouth. The patient then began to vomit copious amounts of blood. At this time the prothrombin was reported as 7 per cent of normal. The patient was given whole blood and vitamin K. The patient went progressively down hill and expired on November 25.

This patient received 120 gm. of Gantrisin.

*Case 4.* An 81 year old white woman was admitted to the Philadelphia General Hospital on November 8, with the complaint of bilateral pain over both costovertebral angles. She was seen by her local physician who prescribed some small white pills to be taken 3 times daily. Her condition became worse and she became feverish and weak, and thus required hospitalization. On admission there was no history of hematuria, frequency, or urgency. Physical examination at this time revealed a well developed, well nourished senile woman who appeared toxic. The patient had marked bilateral costovertebral angle tenderness. The diagnosis on admission was bilateral pyelonephritis, arteriosclerotic heart disease, and pleuritis of the right base.

Laboratory studies on admission showed: Blood urea nitrogen, 7 mg.; hemoglobin, 12.6 gm. per cent; white blood cells, 6,400; urinalysis, 3 plus albumin, 8-10 white blood cells; 2-3 epithelial cells, and a few within 24 hours.

On November 17, gross hematuria developed. At this time the prothrombin time was reported at 19 per cent of normal. Additional laboratory studies showed: Blood urea nitrogen 34 mg.; CO<sub>2</sub>, 37 vol. per cent; chlorides, 568 mg. hemoglobin, 16.4 gm. per cent; platelet count, 134,000; bleeding time, 1 minute; and clotting time, 3 minutes 55 seconds. The Gantrisin was discontinued and the patient was started on vitamin K (2.5 mg. o.d.). On November 21, the prothrombin time returned to 43 per cent of normal and the hemoglobin was 12.8 gm. per cent. The patient's temperature started to rise and she went progressively downhill. She expired on November 24.

The patient received a total of 88 gm. of Gantrisin over a ten day period.

*Case 5.* A 74 year old white man was admitted to the Urologic Service of the Philadelphia General Hospital on August 20 with the chief complaint of back pain and urinary retention. The patient gave a history of frequency and nocturia 5 months before admission, with no history of hematuria, pyuria, or dysuria. Physical examination revealed an elderly white man, with relatively good health. The diagnosis on admission was benign prostate hypertrophy versus carcinoma of the prostate, and cardiovascular disease.

On admission the following studies revealed: Hemoglobin 15.7 gm. per cent; blood urea nitrogen 16 mg.; urinalysis, slight pyuria, white blood cells 11,000; and acid phosphatase 1.05.

On admission the patient was started on Gantrisin (2 gm. 4 times daily). On October 20 the prothrombin time was reported as 16 per cent of normal, although the patient had no hemorrhages or hemorrhagic tendencies. Because of the previous experiences with Gantrisin and associated hemorrhagic episodes, the Gantrisin was discontinued. On October 25 the prothrombin was reported as 34 per cent of normal. On October 31 the prothrombin time was 79 per cent

of normal. On November 3 the prothrombin time was reported as 100 per cent of normal. This patient did not receive any vitamin K or other medication following the discontinuation of gantrisin.

This patient received 296 gm. of Gantrisin.

#### DISCUSSION

The possibility that Gantrisin was the cause of massive hemorrhage due to prolongation of prothrombin time first came to light when the patients in cases 1, 2, 3, and 4 were more closely investigated. Because of the inability to find a blood dyscrasia in these patients, we considered the possibility of a drug toxicity and the only drug that these patients received over a prolonged period of time, was Gantrisin. In all 4 cases, we noted a consistent finding of a lowered prothrombin with normal bleeding and clotting time and evidence of hemorrhagic tendencies.

Case 1 was the first patient who was investigated. This patient had a normal prothrombin which went down to 5 per cent 10 days postoperatively. This patient was on Gantrisin 22 days and received 108 gm. of this drug. Her prothrombin returned to normal in about 11 days after Gantrisin was discontinued and vitamin K was started. This patient showed evidence of liver damage on admission but when prothrombin had returned to normal (after Gantrisin was discontinued), there was no evidence of liver damage. This patient did not exhibit any evidence of agranulocytosis or other blood dyscrasia. A case of agranulocytosis was reported by Hagerman and Franzblau<sup>7</sup> in a patient receiving Gantrisin. The first case we reported led us to investigate further the possibility of Gantrisin as the toxic agent in cases of hemorrhage with prolonged prothrombin time.

Case 2 presents a patient who had hemorrhages in the genito-urinary tract, nasopharynx and from skin cuts sustained while shaving. This patient responded to vitamin K therapy and the discontinuation of Gantrisin. The prothrombin returned 55 per cent of normal in 14 days. This patient received 266 gm. of Gantrisin over a 1½ month period. This patient did not exhibit any evidence of liver damage by laboratory methods.

Case 3 is that of a man who received 120 gm. of Gantrisin over a period of 20 days when massive hemorrhages developed with a prothrombin time of 7 per cent of normal. This patient did not respond to therapy and expired.

Case 4 also presents a patient who had hematuria with a prothrombin level of 19 per cent of normal after receiving Gantrisin 10 days. Her prothrombin returned to 43 per cent of normal but she expired due to cardiovascular causes.

Case 5 represents a patient whose prothrombin was down to 16 per cent of normal after receiving Gantrisin for 2 months. This patient's prothrombin returned to 100 per cent of normal in 14 days after Gantrisin was discontinued. This patient did not receive vitamin K after Gantrisin was discontinued.

In an attempt to prove that Gantrisin was the drug causing hemorrhage in the previous cases, several patients were closely followed with prothrombin,

<sup>7</sup> Hagerman, D. and Franzblau, S. A.: J. A. M. A., 147: 1657, 1951.

liver function tests, blood profile and urinary studies. This study further substantiates the finding of lowered prothrombin with the use of Gantrisin and shows that if this drug is given over a prolonged period of time almost every patient will have a prolongation of prothrombin time.

#### SUMMARY

Five cases have been presented in a preliminary report to show the effect of Gantrisin on the blood prothrombin. Four other cases were studied to further substantiate the evidence that Gantrisin will lower the blood prothrombin, if it is given over a prolonged period of time. The mechanism of the action is not known and further clinical and experimental work will be necessary to substantiate the possibility of liver toxicity. Although sterilization of the gastrointestinal tract with the suppression of prothrombin production is the suspected mechanism, liver damage cannot be excluded.

We believe that Gantrisin should not be given over prolonged periods of time, without closely following the patient's blood prothrombin. We believe that this drug can safely be used over short periods of time (5-10 days) without experiencing any of the hemorrhagic tendency that we have noted.

## EXPERIENCE WITH GANTRISIN AS A PROPHYLACTIC MEASURE IN RHEUMATIC FEVER, WITH SPECIAL REFERENCE TO THE ABILITY OF CHILDREN TO TOLERATE THE DRUG OVER A PRO- LONGED PERIOD

CHESTER M. KURTZ

*From the Department of Clinical Medicine, University of Wisconsin School of Medicine,  
Madison, Wis.*

The numerous publications on the use of Gantrisin in Urology have dealt mainly with the effects of short term therapy. This report on the experience obtained during prolonged Gantrisin therapy in the prophylaxis of rheumatic fever provides data relating to the toxic effects resulting from the administration of Gantrisin over an extended period of time.

It is now a well-established fact that the sulfonamides are highly effective in preventing recurrent rheumatic fever in susceptible children. As a prophylactic measure these drugs are commonly given in small to moderate doses daily without intermission over a period of several years. A few of the sulfonamides have been found more suitable than others and Gantrisin has been reported as being well adapted to this purpose.<sup>1</sup> During the past 3 years the author has had the opportunity of observing closely a group of fourteen children who were receiving Gantrisin prophylactically and the object of this communication is to report on the ability of these children to tolerate the drug over a prolonged period.

### MATERIAL STUDIED

A total of 10 boys and 4 girls all of whom were convalescing from rheumatic fever were studied. With the exception of one boy of  $4\frac{1}{2}$  years, all of the children were between the ages of seven and fourteen. The duration of treatment varied from 3 months to 3 years and the total experience represented approximately thirty-seven patient seasons.\*

The majority of these children were patients in a convalescent home and the remainder were under treatment in their own or foster homes. Gantrisin was started as the rheumatic fever entered the quiescent stage and, with four exceptions, has been continued to the present time. Complete blood counts were taken and the Gantrisin blood level was determined at weekly intervals for the first three weeks of treatment, once every two weeks for the next few months, and then every one to three months whenever the child was seen at the follow-up clinic. Routine urinalyses were made at frequent intervals and these always included a search for sulfonamide crystals in the sediment. Prothrombin determinations were made on nine patients who took the drug over a considerable period of time.

### RESULTS

The results of this study are presented in table 1. The average duration of treatment was 22.4 months. The daily dose of Gantrisin required to maintain a

<sup>1</sup> Bundy, W. E., McCue, C. M. and Porter, R. R. J. Pediatrics, 41: 320, 1952.

\* A "patient season" is the equivalent of one patient taking the treatment for 1 year.

blood level of at least 2 mg. per 100 cc ranged from 0.75 to 2.0 gm. per day with an average daily dose of 1.4 gm. The average blood level for each individual child while under treatment ranged from 2.1 to 4.4 mg. per 100 cc with an average of 3.1 mg. per 100 cc for the group.

In no instance did a significant degree of anemia develop. The hemoglobin readings ranged between 10.8 and 16.0 gm. and were entirely comparable to those of other similar patients not receiving Gantrisin. There was no instance of leukopenia and the total white counts varied for the most part between 4,300 and 14,100. In one patient the leukocyte count dropped temporarily to 3,100 but at the same time the differential was entirely normal. In no case did the total granulocytes (neutrophils, eosinophils, and basophils) drop below 27 and

TABLE 1

| PATIENT | AGE | SEX | DURA-<br>TION OF<br>TRTAT-<br>MENT | HEMOGLOBIN   |              | WBC          |              | TOTAL GRANULOCYTES |              |         | DAILY<br>DOSE<br>GAN-<br>TRISIN | AVER-<br>AGE<br>BLOOD<br>LEVEL | PRO-<br>THROM-<br>BIN<br>TIME |
|---------|-----|-----|------------------------------------|--------------|--------------|--------------|--------------|--------------------|--------------|---------|---------------------------------|--------------------------------|-------------------------------|
|         |     |     |                                    | Maxi-<br>mum | Mini-<br>mum | Maxi-<br>mum | Mini-<br>mum | Maxi-<br>mum       | Mini-<br>mum | Average |                                 |                                |                               |
|         |     |     |                                    | Months       |              |              |              |                    |              |         |                                 |                                |                               |
| M L     | 4½  | M   | 5                                  | 12 0         | 11 0         | 12 3         | 7 3          | 64                 | 30           | 46      | gm                              | mg %                           |                               |
| A W     | 7   | M   | 29                                 | 14 7         | 11 0         | 12 7         | 4 7          | 45                 | 27           | 38      | 1 3                             | 3 3                            | 100%                          |
| E S     | 7   | M   | 31                                 | 14 3         | 12 9         | 11 5         | 4 3          | 70                 | 46           | 58      | 1 0                             | 2 7                            | 100%                          |
| M F     | 7   | F   | 18                                 | 14 5         | 12 9         | 7 4          | 5 5          | 56                 | 37           | 47      | 2 0                             | 3 3                            |                               |
| K S     | 8   | M   | 29                                 | 14 9         | 11 5         | 8 3          | 3 1          | 78                 | 46           | 61      | 1 0                             | 4 4                            | 100%                          |
| R R     | 8   | M   | 25                                 | 15 5         | 11 5         | 9 7          | 4 2          | 90                 | 44           | 59      | 1 0                             | 3 3                            |                               |
| K R     | 8   | F   | 26                                 | 13 0         | 10 5         | 14 1         | 6 8          | 63                 | 31           | 45      | 1 0                             | 3 1                            | 100%                          |
| C W     | 8   | F   | 35                                 | 16 0         | 13 5         | 10 4         | 5 0          | 66                 | 41           | 51      | 2 0                             | 2 1                            | 100%                          |
| J K     | 9   | M   | 30                                 | 15 1         | 12 5         | 10 9         | 6 2          | 62                 | 44           | 50      | 1 5                             | 3 1                            | 100%                          |
| R P     | 11  | M   | 31                                 | 15 0         | 10 8         | 10 8         | 4 3          | 68                 | 33           | 53      | 1 5                             | 2 2                            | 100%                          |
| R J     | 11  | M   | 15                                 | 15 1         | 11 0         | 12 4         | 6 6          | 83                 | 35           | 55      | 2 0                             | 3 3                            |                               |
| R M     | 13  | M   | 3                                  | 13 0         | 11 0         | 9 6          | 5 1          | 65                 | 31           | 50      | 0 75                            | 3 9                            |                               |
| L H     | 13  | F   | 12                                 | 12 9         | 11 6         | 7 6          | 5 0          | 63                 | 50           | 55      | 2 0                             | 3 0                            | 100%                          |
| G R     | 14  | M   | 25                                 | 15 2         | 11 5         | 7 5          | 4 3          | 70                 | 33           | 55      | 2 0                             | 2 6                            | 100%                          |

the average for each child ranged from 38 to 61 which is normal for children in this age group.

Prothrombin determinations were made on most of the patients who had been taking the drug for a year or more and in none of these did the prothrombin time deviate from the normal. The Quick method was used and all of the 9 children on whom this determination was made showed a prothrombin time of 100 per cent.

Every child was given a physical examination twice weekly while under observation in the convalescent home and after discharge was examined in the follow-up clinic at intervals of one to three months. No patient complained of any symptoms which could be attributed to Gantrisin and there were no instances of allergic reactions, skin rashes, ecchimoses or bleeding from any mucous membrane. In no case was it necessary to discontinue the drug because of a toxic or untoward reaction.



## SUMMARY

Fourteen children, 10 boys and 4 girls, ranging from  $4\frac{1}{2}$  to 14 years of age were given Gantrisin daily for periods ranging from 3 months to 3 years representing a total of 37 patient seasons.

The daily dose varied between 0.75 and 2.0 gm. daily.

Prothrombin determinations were made in 9 children who had received an average of 27.5 months of Gantrisin therapy. In each case the prothrombin times were normal.

Gantrisin was well tolerated in every case and there were no instances of toxicity so far as could be determined from history, physical examination, repeated blood counts, blood smears and urinalyses.

## A NEW URETHRAL-URETERAL SPLINT

ARTHUR J. WILETS

*From the Department of Urology, U. S. Naval Hospital, St. Albans, N. Y.*

During the past few years I have been interested in the frequent possibility of contamination from the "Y" tube type drainage of indwelling ureteral catheters. In order to satisfactorily "anchor" the ureteral catheter, it must be fastened to an indwelling Foley catheter, and the two catheters in turn are drained via a "Y" tube or by some similar principle. However, the ureteral catheter becomes easily detached and contaminated. A second danger lies in the ease by which the ureteral catheter can be pulled from its vital position by the thrashing of a patient or by a careless attendant.

To counteract this situation some urologists have guided the distal end of the ureteral catheter through the eye of a Foley catheter and approximately one-half way down the shaft of the catheter. The Foley catheter is then inserted into the bladder and the ureteral catheter thus drains in common with the urethral. In this manner, the danger of infection and/or pulling free of the ureteral catheter is considerably decreased. One objection to this system, however, is a "milking down" action due to the large lumen of the urethral catheter.

The purpose of this paper is to present a catheter which I feel can overcome this difficulty. As is demonstrated in the accompanying diagram (fig. 1), a rubber tube is built into the Foley-type catheter. The tube extends from the proximal end of the catheter to 4 cm. from the distal end. It is built to accommodate up to a 7F ureteral catheter, and due to its elastic nature causes just enough resistance to prevent the ureteral catheter from working down.

Following the introduction of the ureteral catheter, the cystoscope is withdrawn. The distal end of the ureteral catheter is then inserted into the lumen of the new tube and directed about midway down the catheter. With the ureteral catheter thus in place the Foley catheter is then inserted into the bladder in the usual fashion and the balloon inflated.

The patient may be ambulatory by merely attaching the Foley bag-type catheter to a drainage bottle. We find this to be a distinct advantage over the "Y" tube drainage principle in which one encounters the previously mentioned dangers of separation of the ureteral catheter from the "Y" as well as the ever present risk of contamination.

We have used this catheter on a number of occasions, and find it particularly adaptable for strictures or calculi of the ureter. It appears to be of most value in those cases in which one is attempting to overcome an acute condition. For example, it may be used to by-pass a ureteral calculus and afford drainage until the patient is considered operable. If necessary, the ureteral catheter may be

The opinions or assertions expressed in this paper are private ones of the author and are not to be construed to be official or to reflect the views of the Navy Department or the Naval Service at large.

Accepted for publication November 4, 1952.

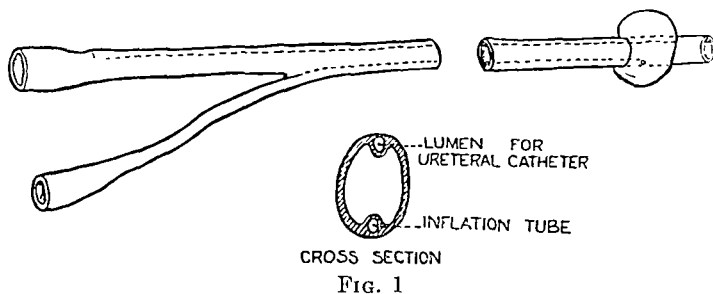


## ERRATUM

P. 619 (October issue): *Memphis, Tenn.* should follow *166 N. Bellevue at Poplar.*

irrigated by inserting either a large gauge needle or a 7F ureteral catheter into the distal lumen of the built-in tube.

It is not recommended that this type of catheter be used in the face of hematuria however, as frequent clots could easily cause an inordinate amount of difficulty in maintaining satisfactory drainage. One other disadvantage is the



inability to observe the ureteral catheter in order to ascertain urinary flow. This latter difficulty is of lesser importance however, as long-term drainage is not being sought by this method.

We would like to emphasize that this appears to be an efficient, inexpensive method of doing away with the "Y" tube drainage principle in acute ureteral emergencies not attended by hematuria. And, as stated above, we have the added advantage of an ambulatory patient.

We wish to express our gratitude to C. R. Bard, Inc., who made these catheters for us and from whom we have received assurance of a continued supply.

## ERRATUM

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## MEDICAL EDUCATION AND TRAINING IN UROLOGY

GEORGE F. CAHILL

The history of the development of medical education in America was, in the beginning, mostly the meeting of emergency demands. In solving the immediate needs for the creation of medical practitioners in the Colonies and in early United States, many difficulties have resulted which are still troublesome problems.

In the early American Colonies, the physicians were usually the clergy for whom medicine was a companion profession, both taught in preparation for service in the Church. In these Colonies for the first century and half from their founding, there was no medical college or any school in which medicine was taught. Only few students among the Colonists could afford to travel to Europe and study medicine. A few did so study and a number later became the leaders in medical affairs.

From necessity and economy the only method of training physicians was by apprenticeship under practicing doctors and clergy. The student accepted by the preceptor learned the art of medical practice by constant companionship, by observation, by some reading and study, but mostly by imitation of his teacher. In this process there was hardly a vestige of science. Patients mostly recovered by their own natural processes.

As the country expanded the demand for physicians increased. Because of travel difficulties this demand was mostly in local communities. With few exceptions, there were no university opportunities to study medicine as existed in Europe and no real hospitals for training. The pressing need for more physicians was met by expansion of the apprenticeship system.

In the beginning of the 19th Century, in the year 1800, less than 10 per cent of the physicians in the United States were graduates of medical schools and more than 80 per cent had never attended a lecture in a school of medicine. To improve this unsatisfactory level of medical practice, medical societies were organized in sections by the practicing physicians to set up standards of preceptor training and examination for membership in these societies. In some states these medical societies controlled the right of medical practice and were given the privilege of granting degrees, and only membership in the society entitled the individual to practice medicine.

Later, physicians in groups banded together and organized themselves into medical faculties. They secured charters from the various state legislative bodies to give medical education and to grant degrees. This type of medical faculty became the fashion and the idea spread rapidly. Its sole support and the faculty income was derived from the students' fees. It is estimated that about 460 various types of medical schools had been chartered at some time or other in the United States and in Canada. In 1800 there were only five medical schools in

Presidential address delivered at the annual meeting of the American Urological Association, St. Louis, Mo. May 13, 1953.



the United States: University of Pennsylvania, founded 1765; Columbia College, founded as Kings College in 1767; Harvard University, 1782; Dartmouth College, 1798; and Transylvania College, 1799. By 1900, the number had grown to 160.

The first convention for the purpose of advancing the standards of medical education was called together in 1846. A second call in the following year 1847 ended in the founding of the American Medical Association. Throughout this period the average preliminary education required for admission was the equivalent of less than a high school graduate. The courses of study in the curriculum varied up to the maximum of three years. There was little change in the period of the pre- and post-war era of 1860 to 1865 and no forward change occurred until the formation of the Association of American Colleges in 1891. From this, the following year (1892) Harvard Medical School changed its course from three to four years. The next year 1893 saw the founding of Johns Hopkins Medical School with a four year course. This was immediately followed by most of the medical schools changing to a four year course which has existed with rare exception up to today.

The Council of Medical Education of the American Medical Association was founded in 1904. With a steady increasing demand for adequate preliminary education, through these years there was a gradual movement, first to demand for admission to medical schools a high school diploma as a minimum and a gradual elevation of the requirements, so that by 1909, seventeen medical schools required two or more years of college work for admission.

In 1910, the Carnegie Foundation for Advancement of Teaching published the study made for it by Mr. Abraham Flexner. This marked the beginning of a rapid change. These changes were produced by the action of schools by themselves, and by the pressure of persons and bodies in the public eye and by philanthropic foundations. Schools with unsatisfactory facilities closed as well as others without the necessary funds and resources to teach the medicine demanded, so that of the 160 schools present in 1905, only ninety-six survived by 1915. The number of students declined with the number of schools as well as the number in the surviving schools. Of the 96 surviving schools in 1915, 85 required either one or two years of college as a minimum preparation before entrance. At the present time every recognized medical school requires at least 2 years of preliminary college work; a large number require at least 3 years and a number a college degree before admission.

It might be proper at this time to call attention to the fact that it was largely not the medical schools themselves that were the initiators of the reforms for the elevation of the standards of admission, but it was often by other professional or non-professional organizations actuated by zeal for public improvement.

This reform for proper preliminary or premedical education has attained most of the objectives desired and has produced a paradoxical result. It was first thought that it would and did reduce the number of students entering into medical schools, and this was considered proper because there was apparently

no shortage of physicians and, instead, better physicians were desired. In the United States there has been present the highest number of physicians per population compared to other nations. In 1930 or so, it was considered that the medical schools graduated an adequate number of qualified doctors to meet the need of the times.

The first change from this was the demand for more doctors by the then administration as a political move for the introduction of some kind of governmental medicine. The resistance of medical education to lowering the then accepted standards only to increase the number of doctors, was quickly overwhelmed by World War II, which came shortly afterward. Here military demands compelled use of facilities to capacity, shortened the curriculum back to 3 years, submerged the faculty and student faculties beyond their capacity to teach and absorb. This has now been realized that though it appeared the wiser thing at the time, it produced less than anticipated and even to this day its results have not been entirely readjusted. Since the last war, the medical colleges have been overwhelmed with applicants far in excess of facilities available for proper medical education. To meet the demand, the changes suggested were either to increase the student class per school or increase the number of schools. Both have proven difficult and slow to arrive at, without deteriorating the level of medical education. A slight increase per class has occurred and a small number of new medical colleges have been established. Adjustment of this problem has been delayed by the Korean episode with its draft of doctors and its demand for more doctors from the resident and the practicing groups and, again, insisting upon an expansion because of the need in the medical schools. In the huge backlog of unaccepted candidates into medicine are those students both well and both not so well prepared. This is largely the problem of the colleges and perhaps now that an extra service penalty having been forced upon medicine by the Armed Forces and with the persistence of the draft in its entirety, medicine looks as if it may be less attractive and a reduction of the number of qualified applicants might occur.

Since the establishment of the four year course in 1892, only rarely have a few schools expanded the curriculum as to time. The expansion of medical knowledge has however brought about a great shuffle within the curriculum. There has been a reduction in the time allotted for older established subjects, to make room for new subjects and approaches. A longer day schedule has been tried as well as the continuation of teaching during the summer sessions. Among the subjects pinched in time have been the old specialities, among which is Urology, and in some schools it looks as if such teaching is to be removed from undergraduate teaching and transferred to graduate teaching.

In all medical colleges revisions of the hours of schedules are in a flux. Since most medical colleges are now associated with teaching hospitals in immediate proximity, the ideal would appear to have in that area courses requiring patient contact and to transfer to preliminary college education those subjects possible to be taught in that atmosphere. A review of timing in education in secondary, colleges and medical schools is needed to allow more time in the medical cur-

riculum. Compared to Europe, secondary education in the United States lags in timing. With the addition of the extension of medical education now universal into residency training and the compulsion of a two year military medical service, some review is needed to save time, if possible, in the now long medical training.

Since the next medical education extension has been in the intern and residency training, this may be discussed with the training of specialists and their effect upon residency training.

Specialties were gradual in their appearance and appeared where centers of population made such possible. Urology, the one that interests us today, began as a specialty somewhere in the middle of the 19th century and was originally an individualist move. Men interested in venereal disease and dermatological conditions began to practice the diagnosis and care of these diseases as a specialty. Their success attracted others and younger men, desiring to become familiar with such concentrated medicine and finding no special educational facilities available for the same, were compelled to become assistant to or work like the former described preceptorship in order to acquire the skill in such a specialty. The demand still increasing, history again repeated, and little specialty school groups were formed under one teacher. A group of teachers, each in a specialty, for convenience and for expansion, then formed groups of medical specialties into medical faculties, apart from universities and established undergraduate schools, and formed the various post-graduate medical schools in the larger cities. The schools first gave short courses and large diplomas; often the shorter the course, the larger the diploma. Gradually the curricula improved and the time of teaching lengthened. Among these specialists were many forceful characters. These characters in each specialty were mostly the founders of many of the national specialty societies. The American Urological Association was formed out of the New York Post-Graduate Medical School by Dr. Ramon Guiteras. At that time, these independent postgraduate medical schools were the only available educational facility for some specialty training.

With the revision of medical education as described previously, established undergraduate schools and independent hospitals began to teach specialty training by extension of internship into residency. To the Johns Hopkins must be given a large part of the credit for this movement.

After the first World War specialty training was slowly extending throughout the country. Its rapid extension however was forced by a movement of independent medical bodies. Among this movement was the action of the American Urological Association, the American Association of Genito-Urinary Surgeons and the Section on Urology of the American Medical Association in forming the American Board of Urology in 1934, patterned after other specialty boards formed in like manner. This Board was incorporated in 1935. It was formed for the purpose of rendering better service to the public by insuring the competency of any physician who is specializing or wishes to specialize in Urology, by examining the candidate and certifying if competent. The Board in its prospectus stated that "it expected to elevate the standards and advance the cause

of Urology." It originally stated that it intended to investigate the curricula of medical schools and encourage adequate facilities for graduate instruction in Urology.

This assumption of power was never actually applied and the investigation of the curricula of medical schools did not occur. The medical schools, state chartered, are under the educational laws of the various states in which they are located. Actually, however, the effect of the Boards, by setting up standards of acceptance of candidates, had a profound effect upon medical graduate education, and this effect was soon apparent. Throughout the country residency training programs were established in the urological departments of the university hospitals, large independent hospitals, veterans, military and public health hospitals. Included in this has been an improvement in the preliminary training before the specialty training as well as in the specialty itself. Facilities are now available for a large number of trainees.

Modification of the standards by the Board has occurred, each modification improving the training. At present, after an internship, an assistant residency in general surgery, surgical pathology, or an equivalent or further training in both as required, is acceptable as preliminary training. A considerable degree of elasticity has been given the candidate in his prespecialty training, according to his talents and intellect. The standards of the Board have brought about a lengthening of the time of residency training and its integration in teaching and the insistence of independent thinking and action in the latter part of the residency. The hospitals throughout the country have slowly changed their residency programs to conform to the standards set up by the Board. There has been a slow but gradual elimination of the ancient apprenticeship and preceptorship. Whether this has been a wise move or not, Time shall tell. For the large majorities of trainees in Urology, the Board has required at least two years in the practice of Urology in the city from which he makes application. Since certification of the Board states its findings as to competency of the certificatee and his fitness to practice, actual practice itself must furnish the experience to determine fitness.

The effect of the Board of Urology, sponsored by the three independent bodies, among which is the American Urological Association, has had a profound effect upon the standards of Urology now in practice. From 1935 to date, 1,808 certificates have been issued by this Board. The Board office has reported 145 deaths since 1935 making a total of 1,663 living urologists certified by the Board. This number has been augmented each year by from 110 to 130 or so new certificatees, this increase to replace the losses and to take care of the increased demand for properly trained urologists and to take care of the expansion of population.

What changes have occurred in Urology since it has become a specialty? Most foremost has been the recession of venereal diseases from within its scope and the transfer of most of that problem into the Department of Public Health. Urology has largely become a diagnostic specialty in all the normal and abnormal functions of the urinary and genitals and allied systems. These have

been so complicated that the former basic pathology training has been now co-sharing with chemistry as the basic training. To the stethoscope and the cystoscope we have added the slide rule. The future urologists will be all mathematicians, physicists and chemists to start. The advances in diagnosis have been numerous. Since the formation of the specialty, we have seen specific curative therapy arrive. Gone is the day when after diagnosis of pneumonia, pyelitis or urethritis was there no specific therapy and the patient recovered due to his own resistive processes. Surgery first offered specific therapy and that was real. More recent the introduction of antibiotics to medicine and surgery has opened the vast field of specific therapy.

As one looks back at the course taken by the urological specialty to advance to where it stands today, it is most satisfying to review with pleasure its contributions to the welfare of the public. Under no circumstances should there be any rest for even now changes are occurring, slowly squeezing urological study out of the undergraduate teaching program into the graduate program only. Advances in medicine have been made mostly within the specialties. An alert urologic specialty has still as bright a future as a past. Also, what of the future? This convention is a practical exhibition of the continuity of education within the specialty. The postgraduate programs and seminars throughout the country are again evidence of progress. It is up to us to explore other methods not only of training and equipping our budding urologists but to keep our accepted certificated urologists moving with medicine as it now progresses. If we do so, then the American Urological Association is performing its proper function. Also, in the rapid change now occurring in medicine and in medical training, we must not lose sight of the broad advance and in any fashion appear to oppose changes even if they appear to the detriment to us as a urological specialty; rather study these changes carefully and if good, join or accept the changes and modify them for betterment. Progress is always present, and with patience and persistency we can keep improving our accepted specialty for the proper training of those who will follow in our footsteps.

*121 E. 60th St., New York 22, N. Y.*

# RECENT DEVELOPMENTS IN LABORATORY AND CLINICAL CANCER CHEMOTHERAPY

ALFRED GELLHORN

*From the Department of Medicine, College of Physicians and Surgeons,  
Columbia University, and the Medical Service of the Francis Delafield  
Hospital, New York, N. Y.*

I have read with interest and vicarious enjoyment of the life of Dr. Ramon Guiteras. His keen delight and exceptional ability in swimming, hiking, riding and other sports give a picture of vibrant physical well-being; his cosmopolitanism is reflected in travel and study in Russia, in the West Indies and in Europe; and his approach to the practice and teaching of Urology which wedded the basic sciences to clinical skill bespeaks wisdom and clear insight into the future of medicine. I am deeply appreciative of this opportunity to give a lecture honoring his memory.

Dr. Guiteras was an enthusiastic big game hunter and it is reasonable to assume that he devoted thoughtful care to the selection of his weapons. Today I would like to trace with you the development of some of the armamentaria designed for the destruction of cancers which are far more hazardous to most of us than anything we are ever likely to meet in the way of wild animals.

Through the centuries the terrifying sight of a patient being consumed by the ungoverned growth of his own tissues has inspired witch doctors and, later, physicians to trials with remedies limited in kind only by the boundaries of the extremely fertile human imagination. Based on fanciful and fallacious concepts of the nature of malignant cells, "drug" treatment of cancer was always worthless and sometimes even harmful.

Precise diagnosis of cancer by microscopic examination; improvement in understanding of the natural history of malignant disease leading to its earlier clinical recognition; impressive progress in curative surgical methods; and the development of radiotherapy as a definitive means to destroy neoplastic cells—all these contributed to the well justified abandonment of drug treatment of cancer by the reputable medical profession at the turn of the century. In spite of the striking advances in diagnosis, surgery and radiotherapy of cancer during the past 50 years however, bitter evidence has convinced clinicians, laboratory investigators and the public of the need for still better control of malignant disease.

How, theoretically, could this be accomplished? Three possibilities come to mind: 1) Simple diagnostic tests which would indicate specific sites of incipient neoplastic growth. The important observations of Papanicolaou on exfoliative cytology constitute a step in this direction; 2) prevention of cancer through removal of those environmental factors which induce abnormal cellular develop-

The Ramon Guiteras lecture presented at annual meeting, American Urological Association, St. Louis, Mo. May 13, 1953.

The research from this department which was reviewed in this lecture was in part supported by an Institutional Grant from the American Cancer Society to Columbia University.

ment. The demonstration of the correlation between cigarette smoking and lung cancer by Wynder and Graham<sup>1</sup> which has been confirmed by other investigators in this country and abroad<sup>2, 3, 4</sup> suggests a means of curtailing the number one cancer killer of men; 3) destruction of disseminated neoplastic disease by systemically administered drugs. Let us focus our attention on research in this last named area.

It is particularly appropriate to review cancer chemotherapy before the American Urological Association because the modern era in this field of investigation was initiated by the brilliant observations of Huggins<sup>5</sup> and of Herbst<sup>6</sup> which led to anti-androgen therapy of disseminated prostatic cancer. This step forward was of great import—not only as a major practical contribution to the management of a frequent malignant disease but also as a demonstration of the vulnerability of the cancer cell to attack through knowledge of its physiological mechanisms.

It would not be practicable to discuss at this time in detail the current status of all aspects of experimental and clinical cancer chemotherapy. In last year's Guiteras lecture, Dr. Huggins presented the contribution of hormones to the problem.<sup>7</sup> We shall confine our discussion, therefore, to the development of several drugs which illustrate the trials, tribulations and satisfactions to workers in the field and also indicate the immediate problems ahead.

In the early 1940's the chemical warfare services of the United States and of our allies were deeply concerned with the development of new chemical warfare agents and of counter measures to chemical poisons known to be in the possession of the enemy. Among the latter was nitrogen mustard, a close relative of the dreaded sulfur mustard "gas" of World War I. Chemical and biological studies quickly led to important insight as to what it did and how it did it.<sup>8</sup> The chemists demonstrated that when nitrogen mustard was put into solution at the pH of body fluids it underwent a molecular rearrangement thereby forming a highly reactive chemical compound. Experiments in the test tube showed that this transformation product would react briskly with compounds containing amino, hydroxyl, carboxyl radicals and other groupings. Simultaneously the biologists were describing precisely the changes in the tissues following administration of toxic doses of nitrogen mustard to experimental animals. They found that lymphoid structures and the cells in the bone marrow were

<sup>1</sup> Wynder, E. L. and Graham, E. A. Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma *J A M A*, **143**: 329, 1950

<sup>2</sup> Levin, M. L., Goldstein, H. and Gerhardt, P. R. Cancer and tobacco smoking *J A M A*, **143**: 336, 1950

<sup>3</sup> Doll, R. and Hill, A. B. A study of the aetiology of carcinoma of the lung *Brit Med J*, **2**: 1271, 1952

<sup>4</sup> Sadowsky, D. A., Gilliam, A. G. and Cornfield, J. The statistical association between smoking and carcinoma of the lung *J Nat Cancer Inst*, **13**: 1237, 1953

<sup>5</sup> Huggins, C. and Hodges, C. V. Studies on prostatic cancer. I. The effect of castration, of estrogen, and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate *Cancer Research*, **1**: 193, 1941

<sup>6</sup> Herbst, W. P. The effects of estradiol dipropionate and diethyl stilbestrol on malignant prostatic tissue *Tr Am A Genito-Urin Surg*, **34**: 195, 1941

<sup>7</sup> Huggins, C. Endocrine factors in cancer *J Urol*, **68**: 875, 1952

<sup>8</sup> Gilman, A. and Philips, F. S. The biological actions and therapeutic applications of the beta-chloroethyl amines and sulfides *Science*, **103**: 409, 1946.

extraordinarily susceptible to destruction by this compound. In 1942 the adventurous leap from the observation of lympholytic effect of nitrogen mustard in dogs and rabbits to therapy of lymphomas and leukemias in human beings was daring indeed. Such a jump was taken by Goodman, Gilman and their associates at Yale and by Jacobson and his colleagues in Chicago.<sup>9, 10</sup> The immediate results of this application of laboratory experiment to human malignant disease were electrifying. Patients with Hodgkin's disease desperately ill with high fever, massive infiltrations of the liver and spleen and unsightly, uncomfortable peripheral lymphadenopathy responded dramatically to intravenous administration of the drug with regression of the evident diseased tissues and marked subjective improvement. Similar remissions were induced in patients with lymphosarcomas. With time and experience it was recognized that the tumor regression was only temporary and that inevitably the manifestations of disease returned. Now after approximately ten years of clinical use the indications and limitations of nitrogen mustard therapy are well defined. No cure of malignant disease has been achieved by this drug; nevertheless it is accepted as a useful agent which complements and supplements radiotherapy in the management of disseminated lymphomas.<sup>11</sup>

This does not tell the whole of the story of nitrogen mustard. Having gone from the laboratory to the clinic it next was returned to the laboratory for further study. Two questions were posed: a) Can the chemists synthesize congeners of nitrogen mustard which will be less toxic to normal tissues, such as the bone marrow, and more destructive of neoplastic tissue? b) What precisely is its mechanism of action against normal and malignant cells and how can this knowledge be used to improve the attack against human neoplasms? With time partially satisfactory answers have been provided by laboratory investigations.

Hundreds of mustard-like compounds were synthesized, tested for their biological activity in experimental animals and a few submitted for clinical trial. Until relatively recently no significant improvement over the original nitrogen mustard was found. Within the past two years, however, a group of drugs, which include triethylene melamine and triethylene phosphoramide (known in the "trade" as TEM and TEPA), have been studied which are useful additions to nitrogen mustard. Unlike the latter compound, which must be given intravenously, the newer agents are active following oral administration. They also produce little or no gastro-intestinal toxicity, a characteristic side reaction of intravenous nitrogen mustard therapy. These are advantages, but it has been learned through clinical trial that qualitatively the action of these newer drugs against neoplastic cells is identical to that of nitrogen mustard.<sup>12, 13, 14</sup>

<sup>9</sup> Goodman, L. S., Wintrobe, M. M., Dameshek, W., Goodman, M. J., Gilman, A. and McLennon, M. T.: Nitrogen mustard therapy. *J.A.M.A.*, **132**: 126, 1946.

<sup>10</sup> Jacobson, L. O., Spurr, C. L., Barron, E. S. G., Smith, T., Lushbaugh, C. and Dick, G. F.: Nitrogen mustard therapy. *J.A.M.A.*, **132**: 263, 1946.

<sup>11</sup> Gellhorn, A. and Collins, V. P.: A quantitative evaluation of the contribution of nitrogen mustard to the therapeutic management of Hodgkin's disease. *Ann. Int. Med.*, **35**: 1250, 1951.

<sup>12</sup> Rose, F. L., Hendry, J. A. and Walpole, A. L.: New cytotoxic agents with tumor-inhibitory activity. *Nature*, **165**: 993, 1950.

<sup>13</sup> Karnofsky, D. A., Burchenal, J. H., Armistead, G. C. Jr., Southam, C. M., Bernstein,



Investigation of the mechanism of action of nitrogen mustard has contributed much to the fundamental knowledge of cellular function and to significant development in the field of cancer chemotherapy. As was mentioned earlier, the chemists had found that, basically, the mechanism of action of nitrogen mustard was dependent upon its chemical reactivity. In determinations of the interreaction between nitrogen mustards and compounds of biological importance it was noted that such diverse substances as amino acids, proteins, a large variety of crystalline enzymes, vitamins, sugars and fats all were modified or inactivated by nitrogen mustard. This offered too many possibilities to account for the observed biological activity and was unsatisfactory. Gradually, however, biochemical, histochemical and morphological evidence was accumulated which pointed to the nucleic acids as the cellular site of action of the mustard compounds.

Let us pause momentarily here to identify the nucleic acids for they will recur frequently in our subsequent discussion. The nucleic acids are complex giant molecules which, joined to protein, are distributed in both the nucleus and cytoplasm of the cell. Chemical dissection of these substances has led to recognition of their component parts, which differ depending upon whether the nucleic acid has been isolated from the nucleus or from the cytoplasm. Their physiological importance was recognized when it was found that the chromosomes of the nucleus contain easily appreciable amounts of nucleoprotein. The dominant role of the chromosomes in cell multiplication and in the transmission of inherited characteristics has long been known and now these fundamental phenomena are beginning to be described in terms of the chemistry of nucleic acids. The nucleic acids of the cytoplasm are apparently of major significance in cellular function. Thus evidence is accumulating which implicates the cytoplasmic nucleic acids in the control of the rate of protein synthesis. More specific description of the function of nucleic acids awaits further research but current knowledge readily assigns to them essential importance in cellular growth, development and reproduction.

To return to the mechanism of action of nitrogen mustards: Cytological experiments have demonstrated mitotic inhibition with specific alteration of chromosomal structure in cells exposed to extremely low concentrations of mustard. Since, you will recall, the chromosome is largely composed of nucleic acids combined with protein, the morphological evidence suggests that the mustards react with these chemical entities.<sup>15</sup> This hypothesis is strengthened by the finding that nitrogen mustard can induce heritable mutations in the fruit fly and certain fungi and can inactivate viruses, particularly those rich in desoxyribonucleic acid.<sup>16, 17, 18</sup> Radioisotope tracer studies have shown depression

J. L., Craver, L. F. and Rhodes, C. P.: Triethylene melamine in the treatment of neoplastic disease. *Arch. Int. Med.*, **87**: 477, 1951.

<sup>14</sup> Gellhorn, A., Kligerman, M. and Jaffe, I.: Triethylene melamine in clinical cancer chemotherapy. *Am. J. Med.*, **13**: 428, 1952.

<sup>15</sup> Bodenstein, D.: The effects of nitrogen mustard on embryonic amphibian development. *J. Exper. Zool.*, **104**: 311, 1947.

<sup>16</sup> Auerbach, C., Robson, J. M. and Carr, J. G.: The chemical production of mutations. *Science*, **105**: 243, 1947.

<sup>17</sup> Stahmann, M. A. and Stauffer, J. F.: Induction of mutants in *Penicillium notatum* by methyl bis (2-chloroethyl) amine. *Science*, **106**: 35, 1947.

of nucleic acid synthesis in the cells of animals given the drug<sup>19</sup> and impairment in the utilization of nucleic acid has been found in other experiments.<sup>20</sup> Thus, at the present time, it is felt that these biologically active drugs disturb the cellular synthesis and/or utilization of nucleic acids, an effect which is incompatible with cell division. These studies on the mechanism of action of nitrogen mustard focused attention on the nucleic acids as a possible site of vulnerability of the cancer cell.

In the story just told the ball was passed from the laboratory to the clinic and back to the laboratory. The development of the folic acid antagonists in cancer chemotherapy follows a different course, for here the initial application was made on the hospital wards and then the laboratory was quickly called upon for help and for clarification of questions.

In 1947 Farber and his colleagues in Boston were studying the effect of a folic acid preparation, teropterin, on patients with neoplastic disease.<sup>21</sup> No significant therapeutic benefit was noted from the drug and, in fact, the course of acute leukemia in children appeared to be accelerated. This suggested the use of a folic acid antagonist in the therapy of the latter disease. All of you have seen during your professional life the heart-rending clinical picture of a child with acute leukemia. You will recall the toxic appearance of the patient, with high fever, bleeding manifestations, splenomegaly, obvious anemia and the typical blood findings. Most of you will also remember that when you went to medical school the only treatment available for this disease was blood transfusions. It is easily understandable then that the report from the Children's Hospital in Boston in 1948<sup>22</sup> which described remissions in this disease produced by the administration of the folic acid antagonist, aminopterin, was greeted as an exciting advance. Soon throughout the country other clinics confirmed the findings in treated leukemic children of a return toward normal of the hemogram, a cessation of purpuric manifestations, disappearance of visceral leukemic infiltrations, a drop of the hectic temperature curve to normal and a dramatic subjective improvement. In the space of 2 years, however, the initial enthusiasm was necessarily tempered by sobering experiences. Thus about 30 per cent of children with the disease failed to show any improvement after treatment. In those that had a remission, the duration was measurable in months and retreatment proved to be progressively less effective with the development eventually of complete refractoriness of the disease to the previously effective folic acid antagonists. How could this be and what could be done about it? These were difficult questions to answer and the aid of the laboratory was obviously desperately needed.

<sup>18</sup> Rose, H. M. and Gellhorn, A.: Inactivation of influenza virus with sulfur and nitrogen mustards. *Proc. Soc. Exp. Biol. and Med.*, **65**: 83, 1947.

<sup>19</sup> Goldthwait, D. A.: Effect of nitrogen mustard on nucleic acid metabolism. *Proc. Soc. Exp. Biol. & Med.*, **80**: 503, 1952.

<sup>20</sup> Ulmann, J. E., Hirschberg, E. and Gellhorn, A.: The effect of nitrogen mustard on the cellular concentrations of nucleic acids in regenerating rat liver. *Cancer Research*, **13**: 14, 1953.

<sup>21</sup> Farber, S., Cutler, E. C., Hawkins, J. W., Harrison, J. H., Pierce, E. C. and Lenz, G. G.: The action of pteroylglutamic conjugates on man. *Science*, **106**: 619, 1947.

<sup>22</sup> Farber, S., Diamond, L. I., Mercer, R. D., Sylvester, R. F. and Wolff, J. A.: Temporary remissions in acute leukemia in children produced by folic acid antagonist, aminopterin. *New England J. Med.*, **238**: 787, 1948

Again basic science illuminated a problem in human disease. In masterfully conceived and conducted experiments Burchenal<sup>23</sup> and Law<sup>24</sup> independently reported the development of aminopterin-resistant leukemic cells after repeated treatment courses and serial transplantation of several experimental mouse leukemias. These observations provided the necessary biological system for unravelling the mystery of the development of human acute leukemia refractory to folic acid antagonist therapy. Law utilized the experimental design of the

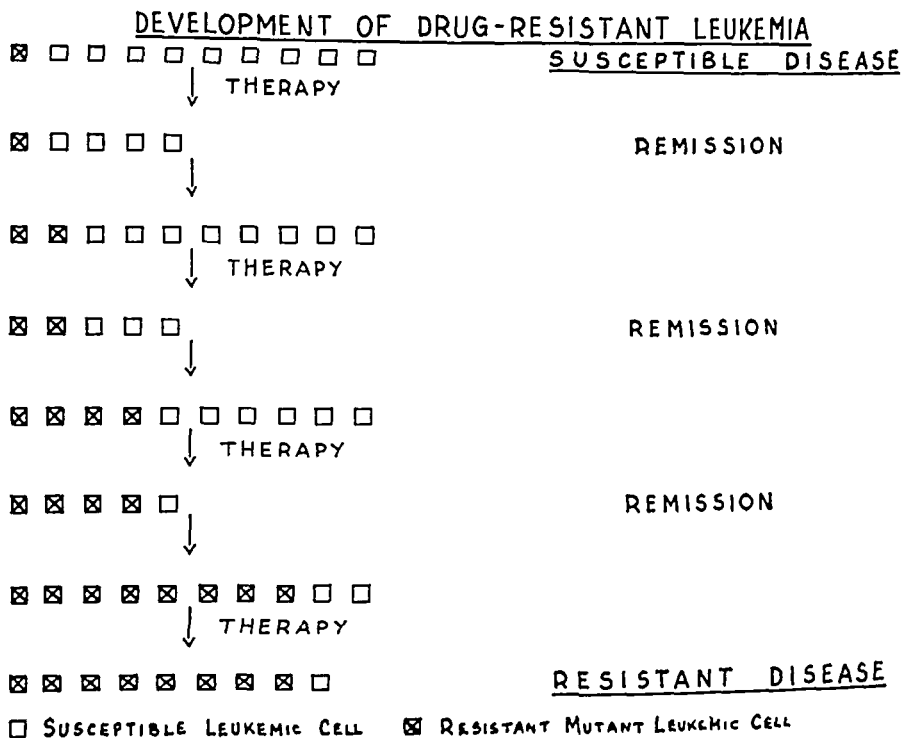


FIG. 1. Schematic representation of development of drug-resistant leukemia by selection of mutant resistant cells during repeated courses of treatment.

bacterial geneticists which had proved so useful in explaining resistance of microorganisms to antibiotics. His results were compatible with the interpretation that in any population of leukemic cells there are present a variable number of mutants which are resistant to antifolic drugs. When treatment is given the majority of susceptible cells are destroyed, but, obviously, the resistant forms are untouched. During a remission both the resistant and susceptible cells multiply until there are a sufficient number to cause a clinical exacerbation of the disease. Retreatment again affects the susceptible cells, leaving the resistant variants untouched. As the cycle is repeated, the proportion of resistant cells increases each time until they constitute the majority of the population. At this

<sup>23</sup> Burchenal, J. H., Robinson, E., Johnston, S. F. and Kushida, M. H.: The induction of resistance to 4-amino-N10-methyl-pteroylglutamic acid in a strain of transmitted mouse leukemia. *Science*, **111**: 116, 1950.

<sup>24</sup> Law, L. W. and Boyle, P. J.: Development of resistance to folic acid antagonists in a transplantable lymphoid leukemia. *Proc. Soc. Exp. Biol. & Med.*, **74**: 599, 1950.

time the disease is refractory to therapy. The sequence of events is schematically represented in figure 1.

These observations on the mechanism of development of drug resistant malignant disease have implications far beyond clarifying the particular problem in acute leukemia of children. It does not seem unreasonable to assume, for example, that the same mechanism is operative in the emergence of prostatic carcinoma cells which are not dependent upon androgen for growth and are therefore refractory to anti-androgen therapy.

The laboratory had now provided the clinic with the explanation for the progressively shorter remissions and eventual failure of response of children

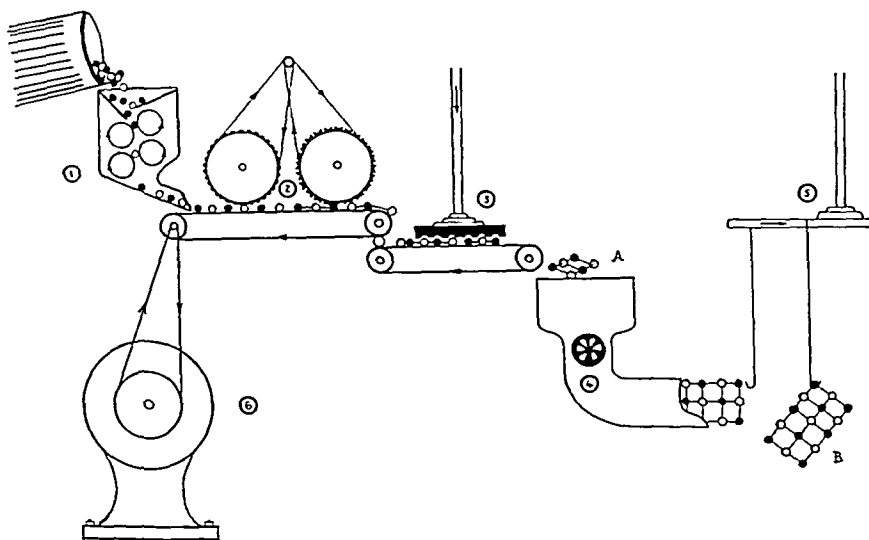


FIG 2 Diagrammatic schema of bio-synthesis of nucleic acids. See text for discussion of numbered processes

with acute leukemia to the anti-folic drugs. Before offering help on how to improve the therapeutic regimen it was necessary to understand the basic mechanism of action of the drugs. The answer was supplied but to savor this exciting accomplishment it is necessary to realize that bacteriologists, biochemists, pharmacologists, microbiologists, biophysicists and nutritionists working on diverse and often apparently unrelated biological phenomena all contributed information which when integrated made a coherent story. As in the case of the nitrogen mustards our attention here also must be directed to nucleic acid metabolism. The steps in the biosynthesis of these giant molecules which are essential for function and reproduction of all cells are complex. Let us attempt to gain some understanding of this fundamental cellular process. In figure 2 we depict an assembly line which is producing nucleic acids. The synthesis starts at Station 1 with the accumulation and sorting of simple and ubiquitous raw materials. These are called precursors and include carbon dioxide, ammonia and the simplest amino acid, glycine. It is necessary to pause momentarily in admiration at this station, for we have learned repeatedly that in the construction

of the many tremendously complex molecules which make up the structures of our body, simple building blocks are invariably used. This reduces to a minimum any work stoppages for lack of appropriate ingredients. At Station 2 the precursors are assembled by a series of enzymatic reactions to an intermediate compound which has been identified chemically. The enzymes which accomplish this process have not as yet been precisely characterized. At Station 3 an enzymatic reaction takes place in which a single carbon atom is inserted into the intermediate compound thereby completing a molecule which is one of the basic components of nucleic acids. The compound represented by A in our diagram is known as a purine. Station 4 is pictured as a large machine whose insides are not exposed at the moment to our view. We do not know the intimate workings of this set of enzymes; we do know that other ingredients, phosphoric acid and a sugar, are added to molecule A and that a number of the new molecules thus formed are put together in infinite variation to form the highly polymerized nucleic acid pictured at B. Station 5 is shown as a conveyor belt and represents the stage of utilization of the nucleic acids in cellular economy. Station 6 represents those reactions which supply the chemical energy to drive the synthetic processes for nucleic acids, proteins, carbohydrates and fats as well as for all other energy-requiring transactions of the cell.

There is a delightful cartoon in the *New Yorker* which shows a blackboard with Professor Einstein's recently published equation summarizing the physical laws of the universe and two admiring physicists. One of the young men says to the other, "Boy, that surely wraps it up!" We assure you that our schematic representation of nucleic acid biosynthesis is not intended to be a "wrapping up" summarization, for there is still much basic research to be done to describe the beautiful series of reactions precisely. Our picture, however, does serve the purpose of helping to visualize where some of the anti-tumor drugs work.

Where do the anti-folic drugs fit into this scheme? You will recall that at Station 3 an enzymatic reaction takes place in which a single carbon atom is inserted into an intermediate to form a purine molecule. This reaction is catalyzed by the biologically active form of folic acid. When the folic acid antagonists are administered they displace the vitamin from the enzyme system and the enzymatic reaction is blocked. The result, which has been documented experimentally,<sup>25</sup> is an accumulation of the intermediate synthesized at Station 2 and a slowing or stopping of nucleic acid synthesis.

While still we have the schema of nucleic acid production before us, let us consider where other strategically placed saboteurs might interfere with the delicate mechanisms. As was indicated earlier, too little is known of the detailed reactions at Stations 1 and 2 for devising biochemical blocks. Station 3 can be tampered with and this has been done. Another site of interference with nucleic acid synthesis is at Station 4. We do not know precisely how the purine molecule A is converted to the polymerized nucleic acid molecule B so we can't alter these mechanisms directly. However, it has been found by biochemists

<sup>25</sup> Woolley, D. W. and Pringle, R. B.: Formation of 4-amino-5-carboxamidoimidazole during growth of *E. coli* in the presence of 4-aminopteroylglutamic acid. *J. Am. Chem. Soc.* 72: 634, 1950.

that if compound A is synthesized in the laboratory and labelled with radioactive carbon or isotopic nitrogen and then administered to animals, it appears in the nucleic acids. This suggested the possibility of tampering with compound A so that it was no longer exactly like the natural purine to see whether the new compound would alter the processes at Station 4.

A number of such purine analogs or antimetabolites have been synthesized. The first one which was found to have activity against experimental tumors was reported by Dr. George Kidder at Amherst College.<sup>26</sup> The compound was closely related to guanine, one of the two purine constituents of nucleic acids. The structural formula of this molecule and of the natural metabolite which it replaces in the synthetic process is shown in figure 3. As can be seen, the only modification of the natural purine molecule which has been made is the sub-

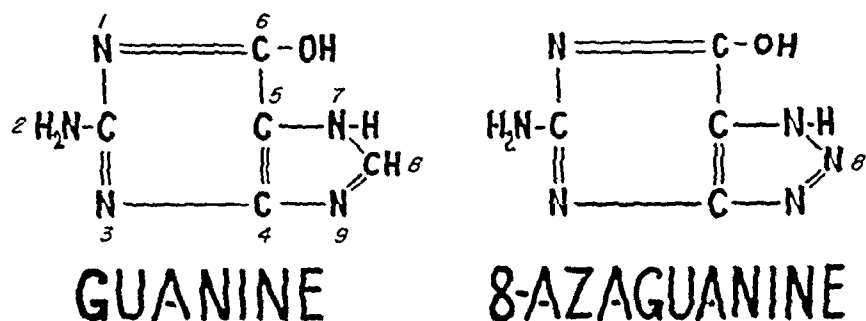


FIG. 3. Structural formula of guanine, a natural purine constituent of nucleic acids and of its analog, 8-azaguanine. Note that change in analog is substitution of a nitrogen atom for a carbon atom in position 8.

stitution of a nitrogen atom for the carbon atom in position 8. When 8-azaguanine, as the guanine analog is called, is introduced into microbiological systems or administered to animals, two things happen to nucleic acid synthesis: 1) the processes at Station 4 are significantly depressed thereby slowing all cellular functions including division, 2) the nucleic acids formed contain the spurious guanine molecule and these unnatural nucleic acids presumably are unable to carry out their functions normally.

One of the tribulations of cancer chemotherapy research is illustrated by 8-azaguanine. In a number of laboratories the compound was found to be effective against a variety of experimental tumors particularly epithelial neoplasms.<sup>27, 28</sup> This raised the hope of workers in the field that a drug might now be available to treat human carcinomas. When the drug was studied in the clinic, however,

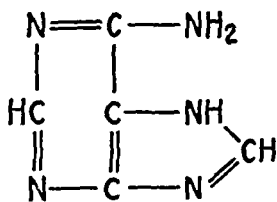
<sup>26</sup> Kidder, G. W., Dewey, V., Parks, R. E. Jr. and Woodside, G. L.: Purine metabolism in *Tetrahymena* and its relation to malignant cells in mice. *Science*, 109: 511, 1949.

<sup>27</sup> Gellhorn, A., Engelman, M., Shapiro, D., Graf, S. and Gillespie, H.: The effect of guanazolo on a variety of neoplasms in experimental animals. *Cancer Research*, 10: 170, 1950.

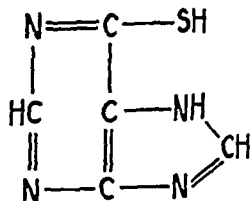
<sup>28</sup> Sugiura, K., Hitchings, G., Cavalieri, L. F. and Stock, C. C.: The effect of 8-azaguanine on the growth of carcinoma, sarcoma, osteogenic sarcoma, lymphosarcoma and melanoma in animals. *Cancer Research*, 10: 178, 1950.

no therapeutic value was observed; in fact, no significant biological activity was noted except the production of skin rashes. How could the discrepancy between the laboratory and the clinic be explained? One investigation of this issue concentrated on the metabolism of the drug in the body. It was found in animal studies that there was an enzyme present in most normal tissues which converted 8-azaguanine to a completely inert compound, 8-azaxanthine. When these observations were then carried over to humans it was found that there was a far greater concentration of the detoxifying enzyme in human tissues than in animal tissues, so great indeed that when the drug was given to man it was immediately metabolized to its inactive form.<sup>29</sup> Thus therapy in human malignant disease with 8-azaguanine was impossible because effective cellular concentrations of the drug could never be attained.

## ADENINE ANALOG



**ADENINE**



**6-MERCAPTOPURINE**

FIG. 4. Structural formula of adenine, a natural purine constituent of nucleic acids and of one of its analogs, 6-mercaptapurine. Note that change in analog is substitution of an —SH group for —NH<sub>2</sub> group in position 6.

In spite of the failure of 8-azaguanine in human cancer therapy, the theoretical considerations seemed entirely valid; so further experimental work was done. The next important advance was reported by Dr. George Hitchings at the Burroughs-Wellcome Laboratory in New York. He synthesized a close relative of adenine, which is another normal purine constituent of nucleic acids, and tested its biological activity on the growth of bacteria. In such a system he was able to demonstrate inhibition of bacterial multiplication and this inhibition could be overcome by the addition of adenine to the culture medium.<sup>30</sup> The chemical structure of the new drug called 6-mercaptapurine, and of the normal component of nucleic acid is shown in figure 4. Again you will note the very slight modification which has been made in the molecule: the replacement of an amino group in the 6 position by a sulfhydryl radicle. It is difficult to conceive that such an apparently insignificant change could have any major biological effect. It very definitely does, however, for not only does 6-mercaptapurine modify the growth of microorganisms but also it has an inhibitory effect

<sup>29</sup> Gellhorn, A.: Laboratory and clinical studies on 8-azaguanine. *Cancer*, 6: 1030, 1953.

<sup>30</sup> Elion, G. B. and Hitchings, G. H.: The mechanism of action of 6-mercaptapurine as revealed by microbiological studies. *Proc. Am. Assoc. for Cancer Research*, 1: 13, 1953.

on experimental tumors<sup>31</sup> and on acute leukemia of humans.<sup>32</sup> At the Sloan-Kettering Institute in New York Dr. Chester Stock and his associates have described the activity of the compound on a variety of tumors. Dr. Joseph Burchenal and his colleagues have reported that remissions in acute leukemia of children, and to a lesser extent of adults, follow the oral administration of daily doses of between one and two and a half milligrams per kilogram body weight. As we look once again at our diagram of nucleic acid synthesis (fig. 2) we can gain some appreciation of the delicacy and precision of the reactions that are constantly in progress. In the case of 6-mercaptopurine just discussed the slight change in component A scrambles the gears, to put it inelegantly, at Station 4.

There is one other fascinating clinical observation which has been made with 6-mercaptopurine. Dr. Burchenal has treated a number of children with acute leukemia whose disease has become refractory to the folic acid antagonists. You will recall that these latter drugs interfere with nucleic acid synthesis at Station 3. It is reasonably presumed that leukemic cells resistant to the folic acid antagonists have some mechanism for nucleic acid synthesis which effectively bypasses Station 3. When children with such resistant neoplastic cells are treated with 6-mercaptopurine, remissions are produced in a significant proportion of the cases. Thus resistance to interference with nucleic acid synthesis at one point in the process does not necessarily imply resistance at other points. This observation has important implications on which we shall touch presently.

The story of the purine antimetabolites shows the candle of knowledge, I hesitate to call it a torch, being passed from the laboratory to the clinic. Let us stop our discussion of specific drugs in the treatment of human cancer at this point and try to assess the significance of these recent developments.

Study of the nitrogen mustards focused attention on the nucleic acids as potentially vulnerable constituents of the neoplastic cell. These compounds have biological activity by virtue of their extreme chemical reactivity. Experimental evidence has shown that the mustards react with chemical groupings on enzymes in Station 4. They also react with the completed nucleic acid, product B, thereby altering its functional capacity; in still other studies it has been found that these drugs interfere with the utilization of the nucleic acids, poorly understood reactions shown at Station 5.

The folic acid antagonists inhibit nucleic acid synthesis at Station 3 by blocking an enzymatic reaction in which the biologically active form of folic acid participates. The purine analogs or antimetabolites can be introduced into the nucleic acid synthetic chain reaction and interfere with the mechanisms of Station 4 or alternatively can be incorporated into the finished product which then proves to be ersatz and of faulty value.

The investigation of the mechanism of action of the drugs mentioned today was dependent upon contributions of all biological sciences to our current under-

<sup>31</sup> Clarke, D. A., Philips, F. S., Sternberg, S. S., Stock, C. C. and Elion, G. B.: 6-Mercaptopurine. an inhibitor of mouse sarcoma 180. *Proc. Am. Assoc. for Cancer Research*, 1: 9, 1953.

<sup>32</sup> Burchenal, J. H., Karnofsky, D. A., Murphy, L., Ellison, R. P. and Rhoads, C. P.: Effects of 6-mercaptopurine in man. *Proc. Am. Assoc. for Cancer Research*, 1: 7, 1953.



standing of cellular physiology. At the same time these compounds have proved to be invaluable tools for furthering that knowledge.

What has been the contribution of the drugs to the treatment of human cancer? It is to be emphasized that no cure has been achieved by any drugs now available. Remissions in disease have been produced permitting periods of happy and useful life to patients with disseminated malignant lymphomas and leukemias which have not hitherto been possible.

Why is only a temporizing effect noted? The limitation of the drugs discussed here today is toxicity to normal cells, particularly those of the bone marrow. The margin between a therapeutic and a toxic dose is too narrow to permit the administration of sufficient drug to destroy the tumor without destroying the host as well. One means of overcoming this limitation is being actively investigated now in the laboratory. We have seen that interference with isolated steps in nucleic acid synthesis temporarily inhibits the growth of malignant tumors. Now a combination of drugs is being employed which sabotages the nucleic acid synthetic machinery at multiple points simultaneously. Results of such therapy against experimental tumors are encouraging and a systematic exploration of such a regimen in clinical cancer chemotherapy can be anticipated.

Another limitation of currently available cancer chemotherapeutic agents, in addition to their toxicity to normal cells, is the small number of tumor types which they affect. The contributions of nitrogen mustard, the folic acid antagonists and the purine antimetabolites lie in the treatment of the malignant lymphomas and leukemias and, to a very much lesser extent, in the management of certain inoperable bronchogenic and ovarian carcinomas. Statistically these constitute a small fraction of all the malignant diseases. In spite of the usefulness of the sex hormones in the treatment of prostatic and breast cancer, there still is a tremendous need for chemical compounds to control disseminated epithelial tumors.

Is there any explanation for this limitation? Two factors should be mentioned. As you know, the rapid advances in the chemotherapy of human bacterial infections which have occurred in the last decade have been dependent in large part upon screening of thousands of compounds against infections in experimental animals or against microbes in culture tubes. Thus if a chemical is found which controls a streptococcus septicemia in mice or tuberculosis in guinea pigs or monkeys or even malaria in ducks, the probabilities are great that it will also be active against the analogous human infection. In cancer chemotherapy screening the compounds are tested against a variety of transplantable tumors in mice, rats and rabbits. However, inhibition or destruction of a mammary adenocarcinoma in mice or a squamous cell carcinoma in rabbits, for example, does not necessarily imply that a similar effect will be noted against the analogous human tumors. In fact the evidence available from clinical evaluations of many compounds which had been found active in laboratory tests suggests that, with the exception of mouse leukemia, animal tumors are not biologically directly comparable to human tumors of the same histological type. Maybe, then, the screening methodology for the selection of drugs active against human malignant dis-

ease could be improved. This major issue is now being investigated and it is conceivable that a more appropriate biological system or several systems will be found.

Another factor which may be operative in limiting cancer chemotherapy largely to the lymphomas and leukemias is the difficulty of clinical evaluations of drugs against epithelial tumors. The lymphomas and leukemias when they are evidently disseminated are most often characterized by rapid progression, marked constitutional reactions, distinctive peripheral blood picture as well as many easily palpable and measurable soft tissue lesions. The signs and symptoms provide ample opportunity for evaluation of efficacy of therapy based on objective criteria. The epithelial cancers, on the other hand, run a relatively chronic course and evaluations based on change of x-ray shadows, alteration in size of soft tissue masses, alleviation of pain or other subjective symptoms are notably unreliable.

Again the path ahead in this problem has been blazed in Urology. It is well-known to you that the demonstration by Gutman of the elevated serum acid phosphatase in disseminated prostatic carcinoma<sup>33</sup> has significantly aided in the development of therapeutic procedures in this disease. Comparable tests for study of therapy in other tumors have not been available. In the past few years, however, attention is increasingly being devoted to this area. Lazlo and his associates, for example, have studied calcium metabolism in patients with osteolytic and osteoblastic metastases.<sup>34</sup> He has found that, under carefully controlled conditions, change in the urinary excretion of calcium is a sensitive and early indicator of the effects of therapy on the tumor. Hyman working on the medical wards of the Delafield Hospital has been investigating the anemia of cancer. He has found that hemolysis plays an important role in the development of anemia in patients with disseminated epithelial tumors as had previously been noted in patients with lymphomas and leukemias.<sup>35</sup> By the use of appropriate techniques it is possible to follow quantitatively the rate of red cell destruction. This measure of the effect of a tumor on host metabolism is now being used in the clinical evaluation of potential chemotherapeutic agents. New objective criteria based on the biology of cancer in man are being widely sought. It is entirely possible that with these available there will be a rapid improvement in the evaluation of drug therapy against epithelial tumors.

What, in summary, can we say of the future of cancer chemotherapy? These are the facts on which to base a forecast. The living cell is a unit of integrated chemical reactions. Each type of cell carries on chemical transactions which are characteristic for it and distinguish it from other cells. When some cells of a tissue grow and multiply while their neighbors have ceased to do so, a change in the chemical behavior of the aberrant cells has taken place. The control of a

<sup>33</sup> Gutman, A. B. and Gutman, E. B.: An "acid" phosphatase occurring in the serum of patients with metastasizing carcinoma of the prostate gland. *J. Clin. Investigation*, **17**: 473, 1938.

<sup>34</sup> Lazlo, D., Schulman, C. A., Bellin, J., Gottesman, E. D. and Schilling, A.: Mineral and protein metabolism in osteolytic metastases. *J.A.M.A.*, **148**: 1027, 1952.

<sup>35</sup> Brown, G. M., Elliott, S. M. and Young, W. A.: The haemolytic factor in the anemia of lymphatic leukemia. *J. Clin. Investigation*, **30**: 130, 1950.

malignant cell other than by complete removal can only be accomplished by controlling its chemical reactions. In our discussion today emphasis has been placed on drugs which alter the essential biochemical reactions of nucleic acid synthesis. This is not the only dynamic mechanism essential to cellular survival. For example we have mentioned the energy producing reactions which are necessary to drive the machinery of nucleic acid synthesis as well as other anabolic processes. As our knowledge of the intimate details of energy production in normal and neoplastic cells is enlarged and as our understanding of the subtle differences in other chemical reactions between normal tissues and cancers grows, chemical agents will be found which can modify the mechanisms and thereby destroy the offending cells. It is not a quick solution which should be anticipated. This is unrealistic and can only lead to disappointment. Not only will we be dependent upon further advances in biochemical knowledge of normal cells but also on characterizations of the chemical reactions of each of the many types of cancers. These advances are being made. The laboratory and clinic are working as a well-integrated team. The forging of our armamentarium is proceeding with ever better blueprints and, I sincerely believe, we can look forward to happier cancer hunting in the reasonable future.

## POLYARTERITIS NODOSA OF THE KIDNEY

HARRY JOEL ZISK

*From the Department of Medicine, Jewish Hospital, Brooklyn, N. Y.*

It is proposed to present in this paper some of the salient features of polyarteritis of the kidney with special reference to its pathologic anatomy and atypical symptoms. It is not within the scope of this paper to review in detail the etiology, pathology and symptoms of the disease, as this information is readily available in any of the numerous publications on the subject, but rather to discuss a few of the more salient factors which should be borne in mind when one is called on to treat this condition. An extensive and detailed review of the literature on the pathology and symptomatology is therefore precluded in this paper so that only a generalized summary of the prevailing conception will be given.

### CASE REPORT

E. L., a white woman aged 28, was suddenly seized with excruciating lower abdominal pains without radiation or fever, of 2 days' duration. She stated that she was well until the onset of the present illness.

Physical examination revealed a well developed and well nourished woman, rather acutely ill. The temperature was 101F and the pulse 100. The heart and lungs were essentially negative; the blood pressure was 120/80. The abdomen was soft throughout, not distended and quite tender all over, but more so in the right lower quadrant; there was no muscle rigidity or rebound pain. No masses or organs could be palpated. Rectal examination was negative. Blood count disclosed a leukocytosis of 12,000 with 30 per cent eosinophiles. No definite diagnosis could be rendered at the time and she was admitted to the Crown Heights Hospital for further study.

On the day following admission several cutaneous nodules, violet red in color, developed over both legs. Each nodule measured approximately 6 mm. in diameter, slightly raised from the free skin surface, and was not tender. A tentative diagnosis of polyarteritis nodosa was made and biopsy of one of the nodules was done for microscopic examination.

Microscopic sections showed a somewhat variegated picture. The epidermis was well preserved. Within the dermis and subcutaneous tissue there were accumulations of round cells, many polymorphonuclear neutrophils and many eosinophiles. These were in the vicinity of small and medium sized arteries and were also present within the vessel walls. The arterial walls were in places necrotic or showed marked fibrinoid degeneration. In some of the arteries there was marked hyperplasia of the endothelium with encroachment upon or obliteration of the lumina. The hyperplastic endothelium in a few arteries was infiltrated with cells as described above. A few multinucleated giant cells were seen in places. The cellular infiltration was also present about the skin appendages and between lobules of adipose tissue (fig. 1). Diagnosis: Polyarteritis nodosa of the leg.

Accepted for publication November 25, 1952.

While in the hospital the patient had progressive weakness and numbness of the feet and legs, and an elevation of temperature which fluctuated between 102 and 99F. On the premise that the lesion may be of an infectious nature, she was given large doses of penicillin parenterally and sulfonamides orally for a period of 10 days, but with no beneficial effects. Soon afterwards, a localized area of gangrene developed on the skin of one leg and was quite resistant to treatment. The skin rash disappeared after 2 weeks; the numbness and weakness however, spread to involve the hands and wrists, and very soon a wrist drop and a foot drop developed. The patient left the hospital after a month's stay with no apparent improvement aside from complete relief of the abdominal pains.

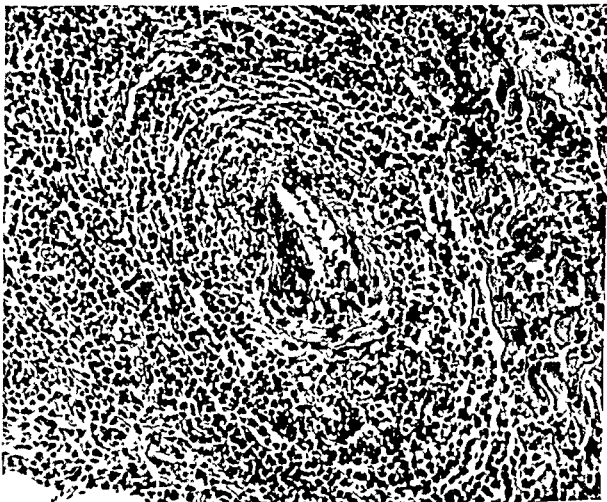


FIG. 1. Biopsy of skin nodule; note necrosis of vessels with marked perivascular inflammatory cell infiltration.  $\times 80$ .

The patient consulted subsequently several clinics including the New York Hospital, Johns Hopkins, and the Brooklyn Jewish Hospital, but very little could be offered in the form of therapy. She continued to linger on for a period of 2 years receiving physiotherapy for the weakness in the extremities, and sedatives for pain. At the end of this time she was readmitted to the Jewish Hospital because of very severe headaches and pain in the back and shoulders, of 3 weeks' duration. She also complained of dizziness, vertigo, nausea and vomiting.

On admission, physical examination revealed an acutely ill patient complaining of severe headaches and back aches. The temperature was 100.2F; pulse 116; blood pressure 200/120. There was some puffiness of the face and around the eyes, and a right foot drop.

Excretory urography revealed normal function on the left with no deformity of the renal pelvis, calyces or ureter. No dye could be visualized in the right kidney. Some calcareous shadows were noted in the upper right quadrant of the abdomen which were thought to be in the gallbladder or in the mesentery.

Cystoscopic examination revealed a trabeculated bladder. The ureteral orifices appeared normal. The right ureter showed an obstruction approximately 20 cm.

from the ureteral orifice in the bladder; no flow of urine was obtained from this ureter. These findings were verified by x-ray examination.

In view of the blockage of the right ureter, probably by stone, an exploratory operation of the right kidney was deemed advisable. At operation, the right kidney was found tense and enlarged to 2 or 3 times the normal. On section, little kidney tissue was noted and clear fluid was obtained. The ureter was not easily visualized. A calcified, ureter-like structure containing numerous beads was noted, the peritoneum was opened and the gallbladder examined; it was free of calculi. A right nephrectomy was performed, following which the pain in the back subsided, the headaches disappeared and the blood pressure dropped from 200 to 160 systolic.



FIG. 2. Kidney removed at operation. Note distension of calyces, pelvis and thinning of cortex.

The gross specimen consisted of the right kidney weighing 88 gm. and measuring 10.5 by 5.6 by 2.7 cm. with 6.5 cm. firm, nodular ureter. The capsule stripped with ease revealing a smooth surface mottled red in the upper pole and pink grey in the remainder. There were numerous petechiae scattered over the surface, more marked in the upper pole. These were also seen in the cut surfaces. The cortex was thin and the pelvis and calyces were greatly distended (fig. 2).

Microscopically, the striking changes were seen in the blood vessels. These changes were typical of polyarteritis nodosa and were seen in all the stages of inflammation, from the acute to the completely healed. In some, the walls were necrotic and densely infiltrated with polymorphonuclear neutrophils and eosinophiles, while others showed less of the cellular infiltration and more of the fibrinoid degeneration in which the wall stained intensely pink. Some of the lumina were occluded by recent thrombi, while others showed organization and recanalization. Still others showed endarteritis, intimal proliferation with markedly

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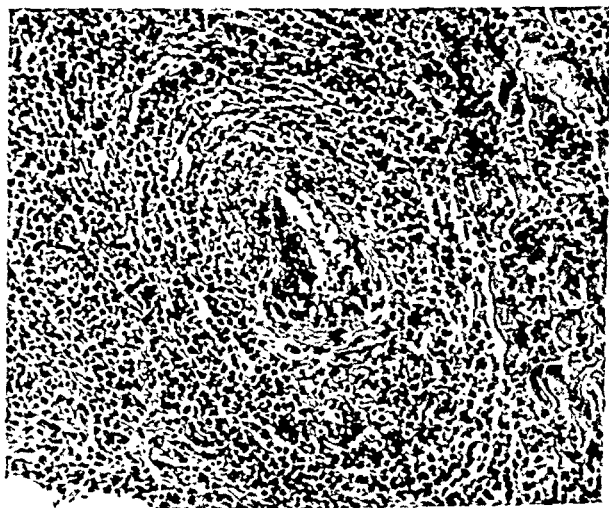


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The patient consulted subsequently several clinics including the New York Hospital, Johns Hopkins, and the Brooklyn Jewish Hospital, but very little could be offered in the form of therapy. She continued to linger on for a period of 2 years receiving physiotherapy for the weakness in the extremities, and sedatives for pain. At the end of this time she was readmitted to the Jewish Hospital because of very severe headaches and pain in the back and shoulders, of 3 weeks' duration. She also complained of dizziness, vertigo, nausea and vomiting.

On admission, physical examination revealed an acutely ill patient complaining of severe headaches and back aches. The temperature was 100.2F; pulse 116; blood pressure 200/120. There was some puffiness of the face and around the eyes, and a right foot drop.

Excretory urography revealed normal function on the left with no deformity of the renal pelvis, calyces or ureter. No dye could be visualized in the right kidney. Some calcareous shadows were noted in the upper right quadrant of the abdomen which were thought to be in the gallbladder or in the mesentery.

Cystoscopic examination revealed a trabeculated bladder. The ureteral orifices appeared normal. The right ureter showed an obstruction approximately 20 cm.

from the ureteral orifice in the bladder; no flow of urine was obtained from this ureter. These findings were verified by x-ray examination.

In view of the blockage of the right ureter, probably by stone, an exploratory operation of the right kidney was deemed advisable. At operation, the right kidney was found tense and enlarged to 2 or 3 times the normal. On section, little kidney tissue was noted and clear fluid was obtained. The ureter was not easily visualized. A calcified, ureter-like structure containing numerous beads was noted, the peritoneum was opened and the gallbladder examined; it was free of calculi. A right nephrectomy was performed, following which the pain in the back subsided, the headaches disappeared and the blood pressure dropped from 200 to 160 systolic.



FIG. 2. Kidney removed at operation. Note distension of calyces, pelvis and thinning of cortex.

The gross specimen consisted of the right kidney weighing 88 gm. and measuring 10.5 by 5.6 by 2.7 cm. with 6.5 cm. firm, nodular ureter. The capsule stripped with ease revealing a smooth surface mottled red in the upper pole and pink grey in the remainder. There were numerous petechiae scattered over the surface, more marked in the upper pole. These were also seen in the cut surfaces. The cortex was thin and the pelvis and calyces were greatly distended (fig. 2).

Microscopically, the striking changes were seen in the blood vessels. These changes were typical of polyarteritis nodosa and were seen in all the stages of inflammation, from the acute to the completely healed. In some, the walls were necrotic and densely infiltrated with polymorphonuclear neutrophils and eosinophiles, while others showed less of the cellular infiltration and more of the fibrinoid degeneration in which the wall stained intensely pink. Some of the lumina were occluded by recent thrombi, while others showed organization and recanalization. Still others showed endarteritis, intimal proliferation with markedly





FIG. 3. *A*, section of kidney showing perivascular inflammatory cell infiltration. Glomeruli here are fairly well preserved  $\times 120$ . *B*, section of kidney showing thickening of Bowman's capsule and arterioles with inflammatory cell reaction  $\times 120$ .

narrowed lumina and with little or no cellular infiltration of the wall; these represented the healing of healed stages or the disease.

The glomeruli in some areas were still fairly well preserved. Elsewhere they showed thickening of Bowman's capsule; many were partly or completely hyalinized. The interstitial tissue was increased in amount and densely infiltrated

with small and large mononuclear cells, polymorphonuclear neutrophils and varying numbers of eosinophiles. The tubules were small and atrophic and contained inspissated, pink staining material. Multinucleated giant cells and cells containing golden brown pigment were also seen scattered throughout the preparations. Some of the tubules also contained calcific material (fig. 3). Diagnosis: Kidney, right, with polyarteritis nodosa, pyelonephritis, chronic and acute; hydronephrosis.

#### COMMENT

Few lesions indeed, present a more variable and complicated clinical picture than those of polyarteritis nodosa, and there is still much discussion and controversy as to the etiology, pathogenesis and methods of treatment of the disease. The lesion often presents a multiplicity of symptom complex which mimics closely one or several diseases of different nature at the same time, rendering clinical diagnosis most difficult. Thus, any one organ or combination of organs in the body may be involved in the disease process at one time leading to almost any combination of symptoms that the imagination can conceive. It is this irregular and baffling symptomatology which has resulted in such chaos of misdiagnosis during life. However, the very protean nature of the disease should lead one to suspect this condition in the differential diagnosis, especially in cases of fever of unknown origin. When the patient first consulted me she presented a clinical picture of an acute inflammatory condition of the abdomen, and cases have been reported in which surgery was performed because of such mistaken diagnosis.

The disease affects all age groups and is equally distributed in both sexes. It is more common however, in young people. There is considerable discussion as to the etiology of the disease. It has been assumed by some that syphilis may be a causative factor. While syphilis may occur in association with polyarteritis, it is nevertheless quite uncommon for the two lesions to co-exist. Although both diseases have one factor in common, namely, that the inflammatory process centers around the blood vessels, the inflammatory reaction however, is widely different in each instance.

Some clinicians have associated polyarteritis nodosa with some allergic manifestations and considerable importance has been attached to the frequent occurrence of allergy in patients with polyarteritis nodosa. It has been assumed that allergy is of primary importance in the genesis of these lesions and cases have been reported of the co-existence of asthma with polyarteritis nodosa. Also, different methods of experimental approach have been used to explain the development of polyarteritis, but some of these are suitable only for animal experimentation. Thus, Harris<sup>1</sup> was able to produce lesions similar in character to polyarteritis in the arteries of rabbits by injecting the animals with bacterial products. One must consider such results with extreme caution since the vascular system of the

<sup>1</sup> Harris, W. H. and Friedrichs, A. V.: Experimental production of periarteritis nodosa in rabbits. *J. Exp. Med.*, 36: 219, 1922.

<sup>2</sup> Rich, A. R.: The role of hypersensitivity in periarteritis nodosa. *Bull. Johns Hopkins Hosp.*, 71: 123, 1942.

rabbit is very labile and subject to great fluctuations when exposed to irritating agents. Rich<sup>2</sup> described vascular lesions characteristic of polyarteritis nodosa in 5 patients who, shortly before death, had hypersensitive reaction following therapeutic injections of foreign serum. The presence of a high eosinophilia in both polyarteritis nodosa and in allergic individuals adds further support to the contention that the two conditions are related. Other observers attribute the cause of the disease to some toxic condition because of its wide dissemination and involvement of almost the entire vascular tree of the medium and smaller size vessels of the body.

At the present time it definitely cannot be stated what underlying abnormality is responsible for the predisposition to the disease. Animal experimentation, although of importance, does not necessarily always apply to changes in the human economy, and consequently experimental efforts should be directed toward human criteria whenever possible. The present state of knowledge permits only theorization regarding the practical application of this experimental work to man. There is no doubt that more than one factor is concerned in the production of this disease; this may be of an infectious, allergic or toxic nature, or a combination of all three. So far as this patient is concerned, there was no history of syphilis, allergy, or infection in the body; although she did develop an intense and prolonged skin rash following therapeutic administration of penicillin.

The onset of the disease, although generally insidious, may be quite acute. Most commonly the patients complain of symptoms referred to the gastrointestinal tract, namely, malaise, anorexia, loss of weight, weakness and general abdominal pains of a vague nature, pain in the muscles of the legs and symptoms of multiple neuritis are frequent complaints. There may be a rise in temperature of a diphasic nature, or the temperature may be normal and irregular. The symptoms may be referred to the heart and cause tachycardia, palpitation, or the clinical picture may be one of acute and chronic glomerulonephritis with evidence of hypertension, nitrogen retention and albuminuria.

Perhaps one of the most significant diagnostic features of polyarteritis nodosa is the disclosure of cutaneous nodules which usually appear over the extremities. A biopsy of one of these nodules will reveal the true nature of the disease. The histologic features of the lesion may be briefly summarized thus: 1) Abundant infiltration with polymorphonuclear neutrophils, eosinophiles, and to a lesser extent also with round cells in and around the small and medium size blood vessels; 2) profound changes in the blood vessel wall consisting of fibrinoid degeneration of the media, endothelial proliferation and thrombosis; 3) fibrosis and recanalization of the vessels. Unfortunately, only a relatively small percentage of the patients with polyarteritis nodosa develop the skin lesion, and one has to search for the lesion in a biopsy of muscle whenever the disease is suspected. There was no difficulty in diagnosis in this patient once the skin rash developed; a biopsy of one of these nodules disclosed at once the true nature of the disease.

The kidneys very often show evidence of acute or chronic glomerulonephritis. Infarctions and massive hemorrhage of the kidneys have been observed and reported. The changes in the kidneys are usually associated with hypertension,

nitrogen retention, albuminuria and hematuria. In the case reported here, one kidney showed widespread destruction and inflammation requiring its removal.

The peripheral blood vessels may show thickening with diminished or absent circulation and pulsation. The changes in the vessels are sometimes associated with local gangrene as it occurred in our patient, or they may give rise to symptoms suggestive of Reynaud's disease. Such findings in the peripheral blood vessels are often suggestive and helpful signs in making a clinical diagnosis. The joints may also become affected and become swollen, tender and red.

The laboratory data are of some aid in making a diagnosis. The blood count shows a leukocytosis and a definite rise in eosinophiles; the latter is frequently reported to average about 7 per cent. Our patient showed an eosinophilia which fluctuated between 60 and 30 per cent. The sedimentation rate is also definitely elevated and at once suggests an inflammatory reaction. The blood chemistry shows nothing pathognomonic aside from nitrogen retention when the kidneys become involved.

The histopathologic changes noted in and about the blood vessels of the kidney are rather unique and quite striking and offer, therefore, little difficulty in diagnosis. The inflammatory process is rapidly progressive and pursues a definite pattern. In the early stages of the disease there is an acute inflammatory cell exudate composed largely of polymorphonuclear neutrophils and eosinophils in and about the small and medium size blood vessels. The intima at the same time shows endothelial proliferation with encroachment on the lumen of the vessel. As the disease progresses there follows in rapid succession, necrosis of the vessel wall and thrombosis of the lumen. The end result of this inflammatory process consists of complete fibrosis and obliteration of the vessel. Sometimes organization and recanalization of the thrombus will occur. We could demonstrate in the same specimen all morphologic gradations, from the early infiltrative cellular tendencies, through endothelial proliferation of the intima, necrosis of the vessel wall and thrombosis, up to frank and unquestioned fibrous replacement of the vessel. It is generally believed that only the arteries are subject to the aforementioned inflammatory changes. It has been shown, however, that the veins may become equally affected. A careful study of a number of sections of both the skin biopsy and the kidney in this patient showed the lesion in both the arteries as well as in the veins. The eosinophils in the inflammatory cell exudate form a striking picture and their presence in large numbers is closely associated with this disease. The necrosis of the media is of a peculiar fibrinoid nature closely resembling the picture seen in Libman-Sacks disease, malignant nephrosclerosis, and rheumatic fever. Indeed, some observers are inclined to associate polyarteritis nodosa with these lesions, although I am more of the opinion that polyarteritis nodosa is a distinct clinical and anatomic entity and should not be confused with any of the other lesions.

The prognosis in patients with polyarteritis nodosa is grave, since very few survive the disease. Life expectancy is usually short and depends largely on the organ or organs affected. When a vital organ is involved, death follows very rapidly. A few patients may linger on for several years, although at no time are

the patients entirely free of symptoms. This patient has been acutely and chronically ill for a little more than 6 years and has been enjoying fairly good health.

Very little can be offered to the patient in the form of therapy. One observer has reported a cure with sulfaphridine administration. We doubt however, that sulfonamides are at all helpful. Our patient received massive doses of penicillin and sulfonamides but with no beneficial effects. Treatment of individual organs as they become involved may become necessary, but complete eradication of the disease cannot be hoped for at the present time.

#### SUMMARY

A case of polyarteritis of the kidney is reported and fully discussed. The case is a typical illustration of the protean nature of the disease, its atypical symptomatology and pathologic anatomy.

The diagnosis of polyarteritis nodosa is difficult at times because of the many organs that may become involved at one time, each with its individual symptom complex.

A correct clinical diagnosis can be made whenever a skin rash is present. A biopsy of the skin lesion will reveal the true nature of the disease.

*164 Argyle Road, Brooklyn, N. Y.*

## A CASE OF RENAL HYPOPLASIA WITH URETER OPENING INTO THE VAGINA

ARTHUR B. CECIL

The mother of a 7-year old child complained that her daughter was constantly wet, although she urinated at definite normal intervals. Nothing else is pertinent in this child's history.

Cystoscopic examination showed a normal left ureteral orifice, but no right ureteral orifice could be seen. With a small endoscope the condition shown in figure 1 was found. Near the cervix and above a slightly constricting band in the vagina, an orifice was seen from which urine was emitted. This opening in the vagina was now catheterized and a retrograde pyelogram made. The tip of the catheter was at the level of the second lumbar vertebra, and the pyelographic medium was about  $1\frac{1}{2}$  cm. beyond the tip of the catheter. Nothing resembling a renal pelvis was made out.

The bladder urine was normal and the phenolsulfonphthalein output from the bladder after 70 minutes was 40 per cent. Since the output of phenolsulfonphthalein from the vagina was infinitesimal, a right nephrectomy was decided upon. The only difficulty about the nephrectomy was in finding the kidney which was in fairly normal position, but extremely small as shown in figure 2.

The pathological report was as follows: "Specimen consists of a small atrophic or undeveloped embryonic kidney which measures approximately 2 cm. from its upper to lower pole, and  $1\frac{1}{2}$  cm. from the cortex to pelvis. The capsule strips without much resistance, except in the region of the pelvis, where it is very adherent. The cortical tissue under the capsule consists of several definite lobulations with numerous less definite minor ones. On one section a contracted fibrous pelvis is seen, and with the aid of a magnifying glass the pyramids and calyces can be made out. Just opposite the pelvis and equi-distant from the pole, there is a bulging well-developed lobe which seems to be more highly developed in the functional elements, tubules and calices, than the tissue at the poles of the kidney. Two sections taken for microscopic study: One through the lower pole, and another through the lobulated area, midway between the poles. Impression: undeveloped, embryonic kidney.

"Microscopic examination: Section 1 (fig. 3) taken from the lower pole of the kidney, shows scarcely any remnants of functional elements. The remnants of the glomeruli are replaced by hyalinization; however, a somewhat normal looking glomerulus is occasionally seen. Elsewhere the specimen is represented by an area of connective tissue, and fibrous stroma, much of which is partially hyalinized. There are numerous and extensive areas of round cell infiltration which contain the remnants of tubules. In one area there is an area of somewhat degenerated epithelium which probably represents a portion of the pelvis.

"Section 2 (fig. 4) is taken from the central portion of the nodular tissue, from the periphery toward the pelvis. In this section normal looking glomeruli are

Accepted for publication December 5, 1952.

numerous, and many descending tubules are seen. There are some areas, however, which show considerable round cell infiltration and near the inner margin there is some connective tissue with small hyalinized areas. This section suggests that the area from which it was taken represented that of a fairly normal kidney in which the functional elements were still patent. Impression: Embryonic undeveloped kidney."

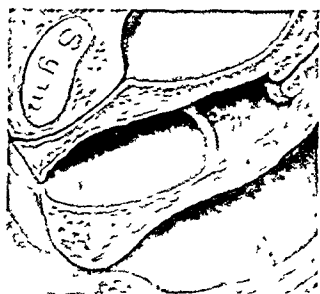


FIG. 1

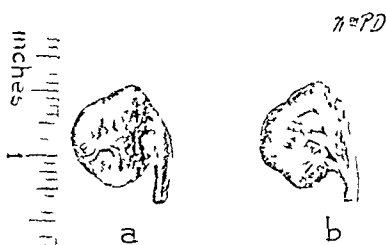


FIG. 2

FIG. 1. Right ureter opening in vagina above constricting band  
FIG. 2 a External surface. b, Sagittal section

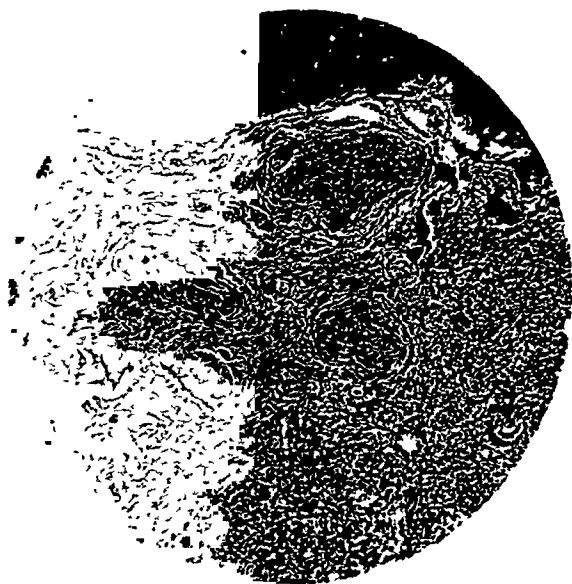


FIG. 3

This case presents two interesting embryological conditions: renal hypoplasia and ectopic opening of the ureter in the female.

I shall first discuss renal agenesis, of which three varieties have been described. First, total absence of the kidney; second, renal aplasia; and third, renal hypoplasia, all of which are defects of development and must not be confused with atrophy of the kidney due to disease.

In total absence of the kidney, the primary renal bud does not develop from the wolffian duct, and so there is no evidence of the ureter on one side.

In renal aplasia, a ureteral orifice is present but the ureter is partly absent or is represented only by a fibrous cord, and the kidney is not a functioning organ, but is represented by fibrous tissue or small remnants of renal tissue.

In renal hypoplasia, a secreting kidney is present, but it is extremely small and is totally inadequate to carry on life. The case which I have presented is a typical example of renal hypoplasia.

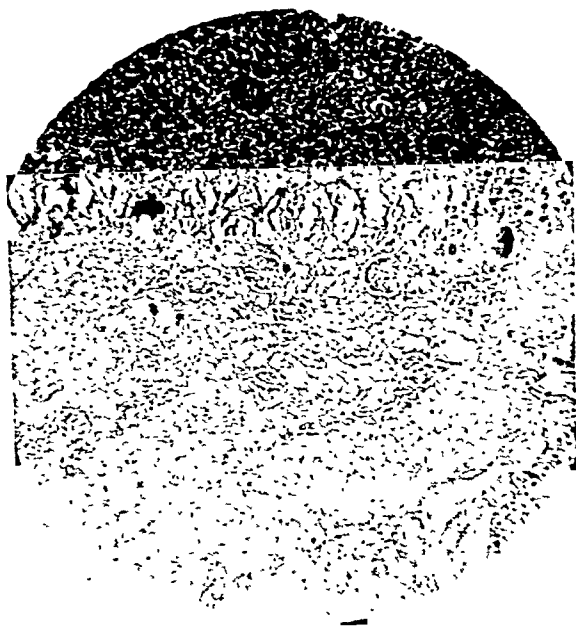


FIG. 4

In all of these conditions, the remaining kidney is hypertrophied. Many writers have called attention to its proneness to disease: stone, pyelonephritis, hydronephrosis, and nephritis. Most writers consider this concomitant disease as due to the kidney having to carry on the entire work of both kidneys. It is not my impression that any such disease processes occur in the remaining kidney after nephrectomy for disease or in cases of unilateral hydronephrosis dating back to very early life.

It is certain that hydronephrosis of the remaining kidney must be due to congenital obstruction. Pyelonephritis and stones may also have stasis as their background in some instances, but it also seems to me that there may be a congenital disturbance of cellular activity, or a tendency to cellular degeneration not due to excessive work but to an inherent weakness; and it seems to me also that in the case of nephritis of the remaining kidney, that this is a congenital



disturbance in the cells, and might not nephritis in general, therefore, be due to an embryological inherent cellular weakness? It is to be hoped that in the future more definite statements as to the diseases of the remaining kidney will be recorded.

The practical point is that in renal agenesis disease is common in the remaining or better kidney, and that frequently the symptoms are entirely on the side of the remaining kidney. Formerly this presented a great hazard, but with the

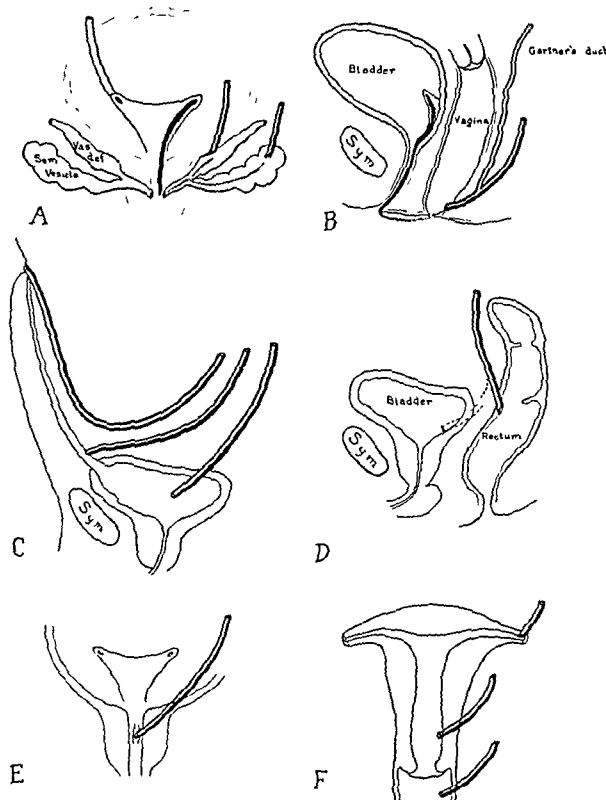


FIG. 5. Ectopic ureteral terminations. *A*, usual embryological path of migration in male. *B*, usual embryological path of migration in female. *C*, unusual migrations to point higher in urogenital sinus or even into allantoic stalk. *D*, urorrectal septum developing anterior to ureteral opening. (Broken lines indicate normal course of ureter.) *E*, unusual migration to müllerian duct in male (uterus masculinus). *F*, migration to müllerian system in female (vagina or uterus, or fallopian tube).

development of intravenous pyeloradiography these hazards are nowhere near what they formerly were, as far as adults are concerned. However, in dealing with children, urological examinations are not easy, and here the danger is very great unless one is extremely vigilant.

The most widely accepted explanation for renal hypoplasia is that during fetal life the kidney, at one stage or another of its development, received an inadequate or improperly distributed blood supply.

In considering the vaginal ectopic ureteral opening in this case, one must recall the close association between the müllerian and wolffian ducts. If the

ureter does not separate itself from the wolffian duct but accompanies that canal in its journey caudalward, there results an abnormal connection of the ureter with those organs which arise from the wolffian duct (in the male, vas deferens, seminal vesicle and ejaculatory duct; in the female, Gärtner's duct). If the ureter does not remain isolated from the müllerian duct, it is attached in women to the uterus or to the vagina. If the ureter, after the sixth week of embryonic life, does not become detached from the wolffian duct but accompanies that canal in its downward course, then the ureteral opening may be found in the urogenital sinus and the organs developing out of this, i.e., in the upper portion of the urethra in both sexes and in the vestibule of the vagina in women. These abnormal openings are graphically illustrated in figure 5.

*1136 W. 6th St., Los Angeles 17, Calif.*

## PERINEPHRIC CYST: REPORT OF CASE ASSOCIATED WITH URETEROPELVIC OCCLUSION AND CONGENITAL HYDRONEPHROSIS

ELMER E. PAUTLER, JR. AND FRED K. GARVEY

*From the Department of Pathology and the Section on Urology, Division of Surgery, Bowman Gray School of Medicine of Wake Forest College and the North Carolina Baptist Hospital, Winston-Salem, N. C.*

Perinephric cysts are rare enough to warrant recording, and yet are of clinical importance due to the differentiation of abdominal masses and to the relief obtained by surgical excision. Campbell<sup>1</sup> states that 12 cases of perirenal hydronephrosis (renal hygroma or hydrocele renis) had been reported up to 1933. Gilliam<sup>2</sup> reported 1 case in 1951 and found only two more in a review of the literature. In 1952 Spriggs,<sup>3</sup> in an excellent paper on this subject, noted that most articles were outside of the English and American journals. From his presentation one must conclude that the number of cases is closer to one hundred or more.

### CASE REPORT

A. P., a 15 month old white male infant, was admitted on November 28, 1951 because of an enlarged abdominal mass, first noted at 2 weeks of age when it was the size of a "duck egg," but had progressively enlarged to the dimensions of a "large grapefruit." There were no associated gastro-intestinal or genito-urinary symptoms except for episodes of crying before urination the 2 weeks previous to admission

The past personal and family histories were not significant.

The physical examination revealed a baby 30 inches in length, and weight 21 pounds, 6 ounces. The diameters of the head, chest and abdomen were respectively 19, 20 and 20¾ inches. The blood pressure was 140 mm. Hg. systolic with a diastolic of 80. The other pertinent findings were restricted to the abdomen which was markedly protuberant. On palpation the abdominal wall was tense and a firm, nontender, lobulated mass was found occupying the entire left side of the abdomen from the costal margin to the pelvis. The impression was a tumor or cyst of the left kidney or adrenal gland.

The laboratory data were as follows: The red blood cell count was 5.2 million per cu. mm. with a hemoglobin of 9.5 gm. per 100 cc of blood and a hematocrit of 35 per cent. The white blood cell count was 10,000 per cu. mm. with a normal differential. Examination of the urine was negative for albumin and sugar with the microscopic study within normal range. The blood Kahn and Wassermann tests were negative. The stool was not unusual. The tuberculin test was negative while the Shick test was positive. Cultures from the throat grew out hemolytic

Accepted for publication November 4, 1952.

<sup>1</sup> Campbell, Meredith: Clinical Pediatric Urology. Philadelphia and London: W. B. Saunders Co., 1951, p. 717.

<sup>2</sup> Gilliam, M. R.: J. Urol., 66: 661, 1951.

<sup>3</sup> Spriggs, A. I.: J. Urol., 67: 414 1952.

staphylococci (coagulase negative). *Pseudomonas*, beta streptococci, and *neisseria catarrhalis*. The blood nonprotein nitrogen was 48 mg. per cent, the chlorides 96.4 mEq. per liter (564 mg. per cent), and the CO<sub>2</sub> combining power 20.3 mEq. per liter (45 vol. per cent).

After whole blood transfusions, the red blood cell rose to 5.9 million per cu. mm. and the hemoglobin was 14 gm. per 100 cc. Three additional urinalyses were within normal range. A chest x-ray was interpreted as normal while a flat

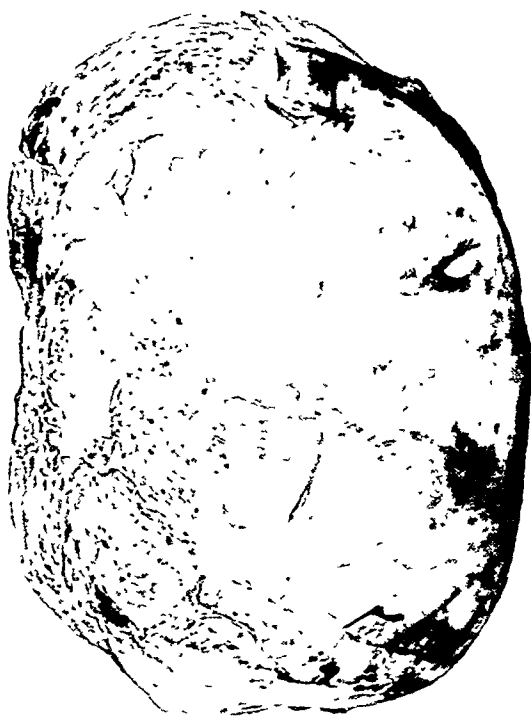


FIG 1 External appearance of perinephric cyst and kidney

film of the abdomen had a large homogeneous density on the left side thought to be a Wilms's tumor. An excretory urogram was considered to indicate good function of the right kidney and ureter but no dye was excreted by the left kidney. The left kidney on retrograde pyelogram was found to be hydronephrotic and pushed downward and to the right by an attached round mass, possibly a cyst. The child at this time had temperature elevations to 104F daily, which were unbenefited by penicillin or chloromycetin but returned to normal after streptomycin. It was felt that an urinary block was present with a renal pelvic infection.

On the twentieth hospital day, under general anesthesia and through a left transverse loin incision, a large cystic mass was removed, which was in the region of the left kidney and attached to the left ureter. The blood loss was

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minimal, but the systolic blood pressure rose to 150 mm. Hg. with a diastolic of 100. The diagnosis was hydronephrosis of the left kidney with a perirenal cyst or hygroma.



FIG. 4. Atrophic renal tissue with perinephric cyst to left and dilated renal pelvis to right H & E.  $\times 13.5$

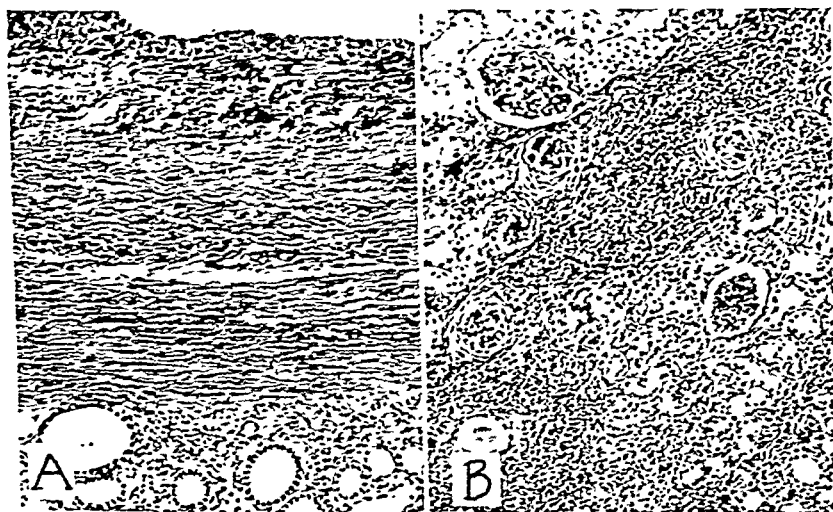


FIG. 5. A, atrophic transitional epithelium of renal pelvis separated from medullary tubules by dense fibrous tissue containing lymphocytes. H & E,  $\times 85$ . B, kidney cortex with atrophic glomeruli and tubules being replaced by fibrous tissue and infiltrated by chronic inflammatory cells H & E,  $\times 85$ .

The gross specimen consisted of a lobulated, encapsulated, greyish-white cystic mass (figs. 1 and 2) which measured 17.5 cm. in greatest dimension. On transection about 1100 cc of clear serous fluid escaped. The mass was composed of two cysts, separated by a thin partition of recognizable kidney which was

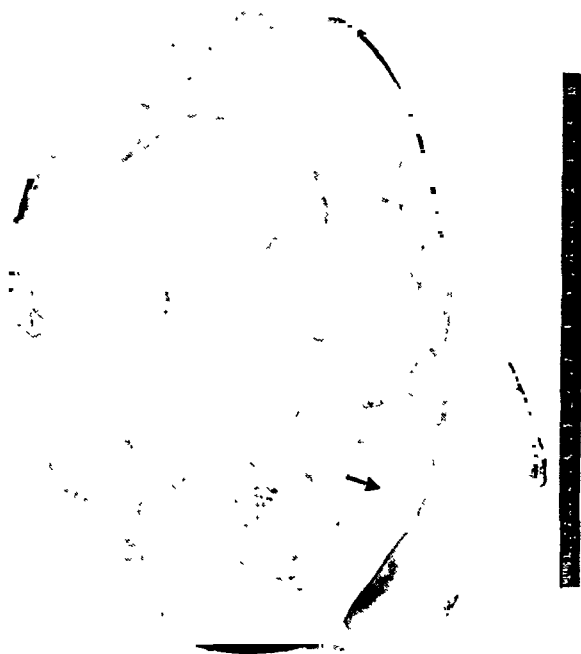


FIG. 2. Cut section with larger perinephric cyst separated from smaller hydronephrotic cavity by partition of kidney tissue. Arrow indicates connecting fistula.



FIG. 3. Superior portion of perinephric cyst with thin layer of adrenal gland separated from fibrous tissue wall by perirenal fat. H & E,  $\times 41$ .

minimal, but the systolic blood pressure rose to 150 mm. Hg. with a diastolic of 100. The diagnosis was hydronephrosis of the left kidney with a perirenal cyst or hygroma.



FIG. 4. Atrophic renal tissue with perinephric cyst to left and dilated renal pelvis to right. H & E,  $\times 13.8$ .

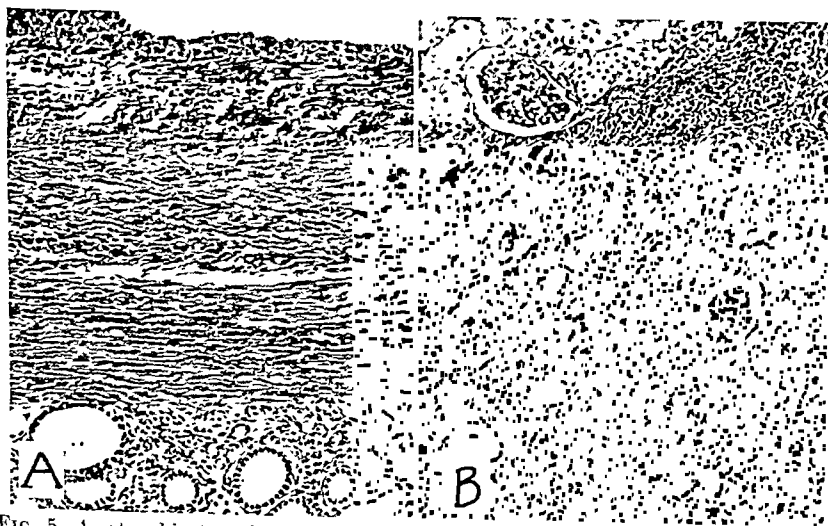


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about 1 cm. in greatest thickness. The larger cyst was about eight times the size of the other, with a 1 cm. fistula connecting them. The cyst linings were smooth, shiny, greyish-white with occasional yellow areas, while the walls varied from 3 to 6 mm. in thickness. Neither cyst had an opening to the outside.

The microscopic sections had the larger cyst wall (fig. 3) composed of a dense fibrous tissue without a definite epithelial lining but infiltrated by many mononuclear inflammatory cells, predominantly lymphocytes. This was surrounded by adipose tissue, and in some areas by a thin layer of atrophic adrenal cortical cells. Sections of the partition of kidney tissue (fig. 4 and 5, *B*) had marked atrophy of the parenchyma, especially the medullary portions, with replacement fibrosis of many tubules and glomeruli. The interstitial tissue was infiltrated by many lymphocytes, plasma cells and macrophages. Many of the arteries were thickened by subendothelial connective tissue. Sections of the smaller cyst (fig. 5, *A*) had a dense fibrous tissue wall with a layer of smooth muscle in some portions, and a diffuse infiltration by chronic inflammatory cells. It was lined by a flattened transitional epithelium, which was desquamated for the most part.

The diagnosis was 1) ureteropelvic occlusion with congenital hydronephrosis and chronic pyelonephritis. 2) perirenal cyst, probably secondary to (1), and 3) atrophic adrenal gland.

The postoperative course was uneventful. The body weight immediately after surgery was 17 pounds, 8 ounces. Urinalysis on four occasions were normal. An x-ray of the left flank was without the previous shadow but was interpreted as having some fluid at the operative site. The blood pressure remained high (168/120) during the first 6 postoperative days, but at the time of discharge on the tenth day, the systolic was 116 mm. Hg. with a diastolic of 84. The parents have failed to return for followup studies on the child but it is presumed that no difficulty has been encountered thus far.

#### COMMENT

Since the abdominal mass was discovered shortly after birth, it in all probability had developed while the child was in utero. The lesion undoubtedly began as a congenital stenosis of the ureteropelvic junction, which eventually became completely occluded. This resulted in the hydronephrosis, and with secondary infection, the chronic pyelonephritis. Because of the presence of the fistula between the dilated renal pelvis and the perirenal cyst, the logical conclusion would be that at some time during the development of the hydronephrosis there was a disruption of the wall with leakage of urine into the parenchyma, and probably the capsule or perirenal tissue. With increasing accumulation of fluid in the perirenal or capsular space, a cyst was formed with resultant stretching and atrophy of the overlying adrenal gland. At the same time the renal cortex and medulla were compressed into an atrophic partition by the combination of intrapelvic and perirenal pressures.

Spriggs,<sup>3</sup> in attempting to reduce the confusion concerning the classification of perirenal cysts, has divided them into three main groups, namely 1) perinephric extravasation of urine, 2) perinephric hematoma, and 3) perinephric

cysts of doubtful origin. We believe this case is an example of the first group, and more specifically of the type of Buerger<sup>4</sup> and Zinner,<sup>5</sup> which have no history of trauma but do have urinary obstruction and a fistula between the hydronephrotic and perinephric cavities. However, in listing 13 cases of the third group, Spriggs<sup>3</sup> found that two were in newborn children associated with urinary obstruction, of which one was due to congenital ureteric stenosis. The cysts in these instances are thought to be the sequela of perinephric bleeding. Campbell<sup>1</sup> states that these cysts are congenital in origin, resulting from a failure of normal tubular obliteration or failure to fuse properly with the excretory ducts.

The cyst fluid is a lymph exudate,<sup>1</sup> but Spriggs<sup>3</sup> believes that the value of such determinations, even when they are made, are equivocal. No analysis was made in this case, but it undoubtedly would have been the same as urine because of the connection with the renal pelvis.

The symptoms<sup>1</sup> in this group of cases are usually abdominal pain with a palpable mass but without alteration of the urinary schedule. This was certainly true in this instance if the "crying at urination" can be considered expression of the pain. Gilliam's<sup>2</sup> patient had hypertension associated with the renal lesion, and the blood pressure became normal following surgery. This child had a preoperative blood pressure of 140/80 with the upper limits of normal being 90/60 for this age group.<sup>6</sup> Although it dropped to 116/84 following the nephrectomy, no additional blood pressures have been recorded up to date.

The diagnosis<sup>1</sup> is seldom made preoperatively, although it was considered in the differential of this case. The pyelograms are usually interpreted as complete ureteropelvic blockage with a malignant tumor considered. It is extremely interesting that in this case hydronephrosis was seen on retrograde pyelogram but there was occlusion of the ureteropelvic junction in the surgically removed specimen. The only explanation is that the stenotic ureter became occluded due to the infection which followed the retrograde pyelogram.

The treatment, according to Campbell,<sup>1</sup> is excision of the cyst, and if necessary, the damaged kidney—presuming however the opposite kidney is adequate in function. The usual procedure is done in two stages: first, drainage of the cyst, and later removal. However, the cyst and kidney were excised in one procedure with good results in this case.

#### SUMMARY

A case of perinephric cyst associated with ureteropelvic occlusion and congenital hydronephrosis is recorded. This is an instance of perinephric extravasation of urine according to the classification of Spriggs.<sup>3</sup> A co-existent hypertension has tended to improve following the nephrectomy. A brief discussion of pathogenesis and clinical aspects is given.

Addendum: Since completion of the paper, a letter from the family indicates that the child is growing and eating well, and without any complaints referable to the abdomen.

<sup>4</sup> Buerger, L.: Cited by Spriggs.<sup>3</sup>

<sup>5</sup> Zinner, A.: Cited by Spriggs.<sup>3</sup>

<sup>6</sup> Holt, L. E., Jr. and McIntosh, R.: *Holt's Diseases of Infancy and Childhood*. New York and London: D. Appleton-Century Co., 1940, p. 557.

## URETEROPELVIC OBSTRUCTION WITH HYDRONEPHROSIS: TREATMENT BY PYELOPLASTY IN 23 CASES

CHARLES N. BURNS, J. EDWIN DREW AND ARCHIE L. DEAN

*From the Surgical Service (Urology Section), Veterans Administration Hospital, Bronx, N. Y.*

Recognition that mechanical factors may produce hydronephrosis has been evident at least since the time of Trendelenburg who about 1886 employed surgery to correct such obstructions. The first successful operation of this type was reported by Kuester in 1892. However, the adoption of renal conservation rather than nephrectomy for the correction of ureteropelvic obstructions was not generalized until the early 1930's. Since then the establishment of certain surgical principles and the advent of antibiotics have substantially improved the results.

Conservation of functioning renal tissue is a fundamental principle of present day urological surgery and on it is based the rationale of pyeloplastic procedures. We believe that practically any kidney in which drainage is anatomically obstructed at the ureteropelvic juncture should be considered suitable for a corrective procedure providing sufficient function remains in that kidney to sustain life. The uncertainty regarding changes which may impair the function of the good kidney as well as the frequent demonstration of how little functioning kidney tissue may be adequate to sustain life encourage the efforts to improve the status of a obstructed kidney.

The purpose of this report is to summarize our experience in the surgical treatment of 23 ureteropelvic juncture obstructions.

### SELECTION OF CASES

The proper selection of a patient for conservative surgery depends upon the accurate diagnosis of a persistent organic obstruction sufficient to cause progressive hydronephrosis in a kidney which retains sufficient function to sustain life and which is not affected by some other disease which would require nephrectomy. These factors may ordinarily be determined by:

- 1) Excretory and/or retrograde pyelography which visualizes the characteristic deformity of pyelectasis and caliectasis proximal to an area of obstruction located at the ureteropelvic juncture.

- 2) The amount of remaining function as indicated by the promptness of the appearance and the concentration of the contrast medium on excretory pyelography.

- 3) The thickness of parenchyma visualized on the pyelogram.

- 4) The delay in emptying or pelvic retention shown by a "trapping film" taken 10 minutes after retrograde injection of contrast medium. Unobstructed kidney pelves should empty within this time.

Ordinarily these studies are sufficient to permit a decision but occasionally

Accepted for publication December 5, 1952.

more searching tests are required to substantiate suggestive findings. These individually or collectively are:

- 1) Appearance time and ten minute comparative ureteral catheter specimens of phenolsulfonphthalein given intravenously.
- 2) Cystoscopic evaluation of the appearance time and concentration of indigo carmine given intravenously.
- 3) Urea content and specific gravity of comparative ureteral specimens.
- 4) Microscopic and culture studies of separate kidney specimens.
- 4) The size, number and location of calculi.
- 6) In borderline cases, evidence of the progress or equilibrium of the hydronephrotic process observed over a period of time.

In general, any impairment of the opposite kidney emphasizes the necessity for salvaging the hydronephrotic kidney; while additional adverse factors in the hydronephrotic kidney might lead to its removal if the remaining kidney is entirely normal. Not infrequently final evaluation of the status of the diseased organ was only provided by surgical exploration.

#### SURGICAL CONSIDERATIONS

When surgery was deemed advisable the kidney was approached extraperitoneally by whatever incision seemed most likely to provide adequate exposure and permit the inspection of the site of obstruction before it was altered by manipulations. If the organ was found sufficiently "sound" to warrant pyeloplasty all extraneous factors such as bands, kinks, vessels and excess mobility were appraised and corrected, if possible. The residual fullness of the renal pelvis was then observed. Failure to collapse or drain freely after these measures prompted further investigation after pyelotomy. Direct inspection and calibration of the ureteropelvic juncture was then done. If a 12F soft rubber catheter passed easily, a plastic procedure was usually considered unnecessary but failure of such a catheter to pass showed the need of some type of correction. Commonly the area of narrowing begins at the ureteropelvic juncture and extends for varying distances down the ureter. The extent of the narrowed segment rather than its calibre should determine the type of repair necessary. Extreme narrowing of a segment of ureter no more than 1 cm. in length can be corrected by resection and ureteropelvic anastomosis. The Foley Y-V type repair was found applicable with stenosis up to 2 cm. in length and was our most commonly employed method. With narrowed areas longer than 2 cm. intubated ureterotomy was performed with the incision either through the mucosa as Davis suggests or down to mucosa after Ramstedt with either single or multiple incisions. The ureter was splinted through and well beyond such incisions and nephrostomy or pyelostomy drainage was used in addition. Redundant pelves were resected to reduce residual urine and perhaps improve dynamics.

Certain surgical principles were closely followed. Because most factors affecting wound healing depend on the blood supply, special attention was given to preserving existing vessels, providing adequate pedicles for flaps, avoiding tissue tension and controlling infection. Complete delivery of the kidney was avoided

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unless nephropexy was required. The perirenal fascia was ordinarily utilized as a sling to stabilize the site of the plastic procedure as well as to diminish excess mobility of the kidney.

#### POSTOPERATIVE TREATMENT

In addition to the general surgical postoperative care, a detailed scheme of specific urologic management was followed. This included routine use of antibiotics; trained personnel to supervise the tubes, dressings and irrigations and a calculus prophylaxis regimen which followed the Schorr principles\* and included irrigations with an acid solution.

The splinting catheter was removed (as in the Foley Y-V) in 2 weeks in clean cases in which primary wound healing was anticipated. Clean cases which had not been primarily approximated (intubated ureterotomies) were splinted for four weeks. Pre- or postoperatively grossly infected cases were left intubated for 6 weeks.

Before the nephrostomy or ureterostomy tube was removed roentgenographic studies were made. Plain films were taken in search of calculi and antigrade pyelograms were made to measure the adequacy of the lumen, failure to heal, and amount of "trapping." Evidence of calculus or incrustation called for increased acid irrigation; inadequate lumen required inlying ureteral catheter (introduced cystoscopically) whereas leakage through the suture lines suggested that pyelostomy or nephrostomy drainage be continued. We prefer separate tubes for splinting and drainage because this permits removal of the splint while urinary diversion may be retained.

A successful operation usually is followed by prompt closure of the drainage fistula although such closure is no warranty of a good result. Soon after closure of the fistula excretion urograms are made. Ordinarily this and urine studies for evidence of continued infection will provide all the necessary information to direct further treatment whether surgical, instrumental or merely continued observation.

#### FOLLOW-UP

These patients should be closely observed until the urine is clear and sterile and the pyelogram stabilized at what appears to be its optimal condition. While in most instances the pyelogram will show some improvement, a return to normal is seldom anticipated. In fact, should it occur, it would indicate that no true hydronephrotic parenchymatous damage had been present. Earlier appearance time of contrast medium, more prompt emptying and a flaccid rather than tense appearance of the renal pelvis and calyces should be apparent in good results.

Disappearance of infection is a concomitant of good drainage. A clear urine and any degree of pyelographic improvement presage the end of the hydronephrotic process and a clinical symptomatic improvement. Infection preoperatively usually caused delay in sterilization postoperatively. The persistence of

\* Schorr, E. and Carter, A. C.: J.A.M.A., 144: 1549-1551, 1950.

infection for 6 months following operation without other symptoms or signs calls for complete re-study of the kidney.

## STATISTICAL DATA

TABLE 1. *Incidence (during 4 years)*

|                                                                     |       |
|---------------------------------------------------------------------|-------|
| A Number of operations                                              | 23    |
| B Age (20-57) average                                               | 27.2  |
| C Number of bilateral cases                                         | 3     |
| D Right side                                                        | 11    |
| E Left side                                                         | 12    |
| F Patients admitted to the G.U. service during this period          | 2,449 |
| G Number of hydronephroses requiring nephrectomy during this period | 8     |

Twenty patients had 23 operations in the course of 4 years by eight resident surgeons (table 1). These patients were all males, the hospital having a high preponderance of this sex. The patients' ages ranged from 20 to 57 with an average of 27.2. Despite the congenital origin of these obstructions, the changes are so insidious that usually symptoms do not occur before the third decade of life. There is a tendency for these lesions to occur bilaterally, though when found, they have usually progressed to a different degree in the two kidneys.

TABLE 2. *Symptoms*

|                            |    |
|----------------------------|----|
| A. Posterior lumbar pain   | 15 |
| B. Anterior abdominal pain | 4  |
| C. Low back pain           | 1  |
| D. Urinary symptoms        | 2  |
| E. Asymptomatic            | 1  |

In this series the salient symptoms were localized in the respective renal area in most cases and consisted of pain of varying degrees (table 2). In a number of cases the pain was anterior abdominal and frequently interpreted as originating in the intestinal tract. In still fewer cases the disease was manifest by urinary symptoms such as frequency and dysuria; hematuria being present in one case.

TABLE 3. *Pathological anatomy*

|                                             |    |
|---------------------------------------------|----|
| A Congenital stenosis                       | 16 |
| B Extrinsic factor plus congenital stenosis | 5  |
| C High ureteral implantation                | 1  |
| D Unclassified                              | 1  |

In most instances the hydronephrosis resulted from a congenital stenosis per se (table 3); these narrowings being congenital and not strictures resulting from scarring. Several existed in combinations with extra-luminal factors such as aberrant vessels, bands, adhesions, kinks or ptosis. However, when extrinsic factors are found, the possibility of intrinsic causes should not be overlooked. One patient (fig. 1) in this series was operated upon and an aberrant vessel severed with no alteration in the symptoms or degree of hydronephrosis. Repeat studies



and surgery 2 months later revealed an intrinsic lesion. This intraluminal narrowing was then treated by intubated ureterotomy with prolonged drainage and splinting. The result was complete reduction in the hydronephrosis and alleviation of symptoms. "It is all too familiar that severing aberrant vessels in certain cases results in temporary or no improvement."\* The cause of the hydronephro-

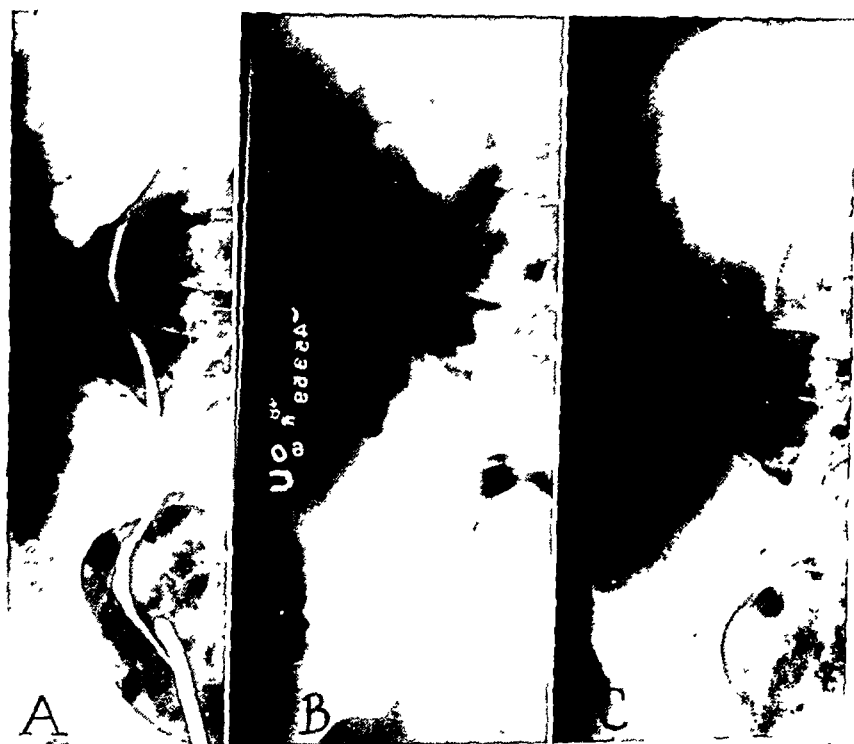


FIG. 1. White man aged 26 complained of constant dull pain in right lumbar region for 2 years. *A*, right ureteropyelogram demonstrating "derby hat" type of pyelogram with sharp line of demarcation at pyelo-ureteral area. *B*, 60 minute excretory urogram 2 months after removal of aberrant vessel. Pyelogram, performed after there was no alteration in symptoms, discloses persistent pyelectasis and caliectasis without sharp "cutting off" effect. *C*, 60 minute excretory urogram after intubated ureterotomy procedure, as advocated by Davis.

sis in one case was considered to be a "high implantation" of the ureter into the renal pelvis, but a stenosis was also present. Careful ureterolysis in two cases revealed an extreme degree of external as well as internal narrowing. In another case the operator failed to describe the pathological changes.

TABLE 4. *Type of plastic repair*

|                                                      |    |
|------------------------------------------------------|----|
| A. Foley Y plasty                                    | 17 |
| B. Intubated ureterostomy (Davis)                    | 4  |
| C. Intubated ureterostomy (Ramstedt)                 | 1  |
| D. Ureteropyeloneostomy after segmental section. . . | 1  |

The selection of the method of repair was made at the time of operation and was dependent on the length of the narrowed segment. Because of the shorter

\* Henline, R. B. and Menning, J. H., *J. Urol.*, 50: 1, 1943.

period of drainage required when the plastic repair was sutured, this method was used where possible rather than the non-sutured splinted ureterotomies.

TABLE 5. *Type of drainage*

|                                         |    |
|-----------------------------------------|----|
| A. Nephrostomy                          | 15 |
| 1. McIver tube                          | 8  |
| 2. Separate drainage splint and tubes   | 5  |
| 3. "T" tube                             | 2  |
| B. Pyelostomy all with separate splints | 8  |

The splint and drainage tubes were allowed to remain in situ for an average of 29.2 days in 20 cases. The time of splinting and drainage is dictated by type of repair but it may be modified by whatever complications may arise. Smaller splints for shorter times consistent with good results is the present goal in closed cases. Separate tubes for each purpose are now used. Where an adequate pelvis permits, a pyelostomy rather than nephrostomy is employed.

TABLE 6. *Tube irrigation*

|                                          |    |
|------------------------------------------|----|
| A. None                                  | 5  |
| B. Suby's solution                       | 14 |
| C. Normal saline                         | 3  |
| D. Acetic acid ( $\frac{1}{2}$ per cent) | 1  |

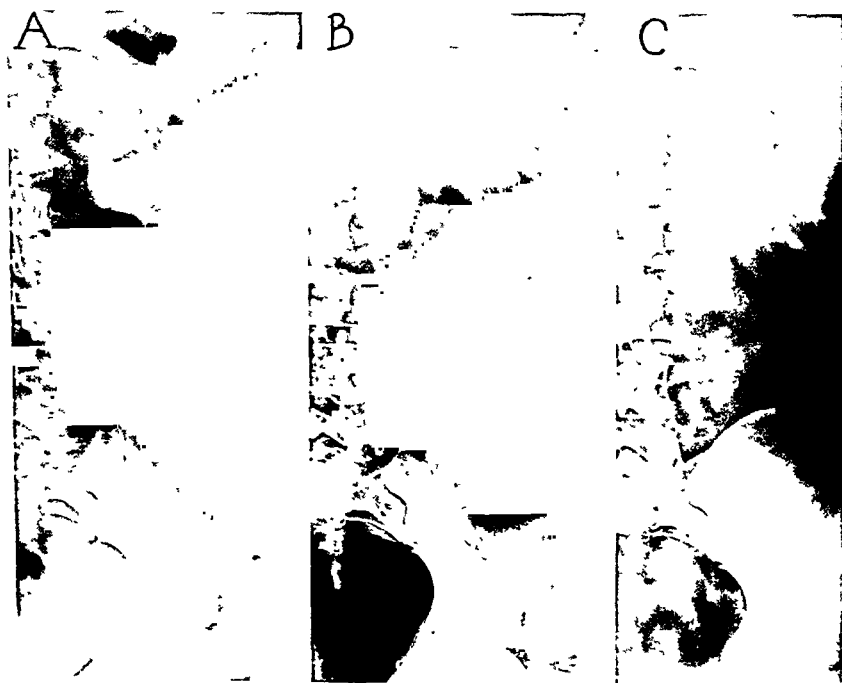


FIG. 2 White man aged 24 complained of frequent intermittent left lumbar backaches for 2 years. A, pyelectasis with caliectasis. B, calculus formed about upper limb of "T" tube which was irrigated with saline after Ramstedt type pyeloplasty. C, result 6 months after left nephrostomy and nephrolithotomy.

Acid irrigation of the tubes seems to be an important factor in preventing incrustations and calculi (table 6). In one instance in which a "T" tube was used and irrigated daily with saline, a calculus formed on the upper limb requiring a temporary nephrostomy and subsequently a nephrolithotomy (fig. 2). Consequently, the last 14 patients were irrigated every 6 hours by bulb syringe with Suby's solution at the first sign of a precipitate in the urinary drainage and no incrustations were observed subsequently. T tubes are no longer used.

TABLE 7. *Infection*

|                   |                         |
|-------------------|-------------------------|
| A. Preoperatively | 9 cases                 |
| B Postoperatively | 11 cases (5 of above 9) |

Infection alone pre- or postoperatively posed no insuperable problem with modern chemotherapeutic agents and antibiotics (table 7). However, in many cases preoperative diagnostic instrumentation was deferred until the day before

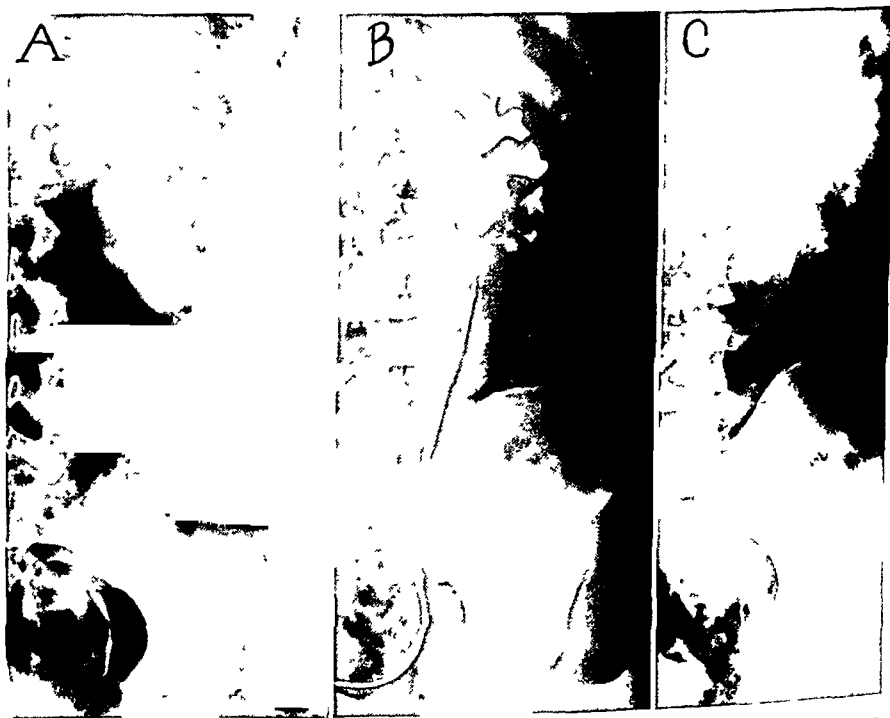


FIG. 3. White man aged 21 complained of left lumbar pain of 3 months' duration. A, left ureteropyelogram 10 minutes post injection disclosing marked hydronephrosis. Preoperatively considered to require nephrectomy B, pyelogram 2 months post Foley "Y" plasty and Deming nephropexy for stenosis at ureteropelvic juncture, aberrant vessels and ptosis C, 30 minute urogram 7 months after surgery. Three year postoperative excretory urogram shows slight improvement over C.

surgery or an indwelling catheter in the renal pelvis was allowed to remain in situ in order to prevent converting a hydronephrosis into an infected hydro-nephrosis. All of our patients were given chemotherapy and antibiotics pro-

phylactically or to treat demonstrable infection. During the period of postoperative intubation contamination was evident in all cases when a culture was taken. Positive cultures however were not ordinarily associated with fever or gross pyuria. Infection, when the anatomical end results were good, usually abated about 3 to 6 months after surgery. It required 9 months after the pyeloplasty shown in figure 3.

TABLE 8. *Diet*

|                               |    |
|-------------------------------|----|
| A. Regular                    | 12 |
| B. Low calcium and phosphorus | 11 |

The restrictions of a low calcium and low phosphorus diet were not always imposed on these patients during their early convalescence (table 8). If they had had calculi preoperatively or were excreting a large amount of phosphate postoperatively such a diet plus aluminum gel was used as early as feasible.

TABLE 9. *Pyclographic results*

|                            |    |
|----------------------------|----|
| A. Improvement             | 19 |
| B. Required nephrectomy    | 1  |
| C. May require nephrectomy | 2  |
| D. Inadequately followed   | 1  |



FIG. 4 Negro aged 33 complained of pain on left side of abdomen and lumbar region for 1 month. A, multiple left renal calculi. B, pyelogram demonstrating caliectasis without marked pyelectasis. C, 10 minute delayed post operative film with calyceal trapping without pyclographic medium in pelvis.

All cases showing good pyelographic results were symptomatically improved (table 9). One patient continued to have pain postoperatively. His kidney showed gross infection and was removed but without symptomatic improvement. He had had a duodenal ulcer for twenty years and his condition failed to improve until a gastroenterostomy was performed. (This raises the question as to whether the kidney might not have been salvaged.) Of the two cases that may require nephrectomy, one with infection, calculi and an intrarenal type pelvis has not responded favorably to the plastic repair (fig. 4). The other has shown a poor

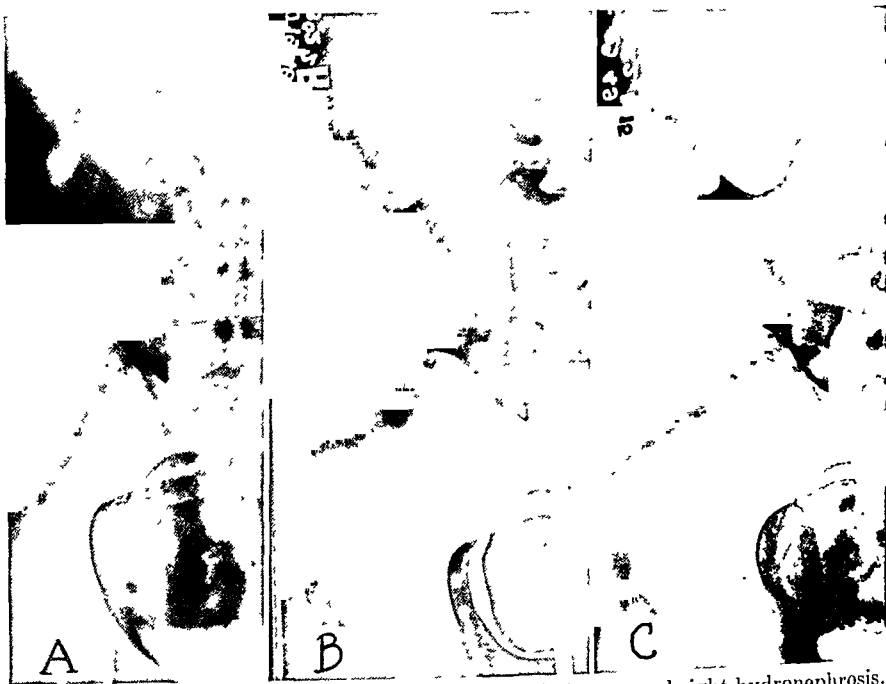


FIG. 5. White man aged 26 with history of perineal abscess and right hydronephrosis, as revealed by excretory urogram. *A*, 60 minute preoperative excretory urogram revealing caliectasis with pyelectasis and narrowing at ureteropelvic junction. *B*, right ureteropyelogram 2 months postoperatively. *C*, right ureteropyelogram (15 minute trapping film) showing no alteration in degree of hydronephrosis or narrowing at ureteropelvic junction.

result pyelographically as well as symptomatically. *Aerobacter aerogenes* organisms are being cultured from the operated side on repeated follow-up studies. Microscopic examination of the urine shows considerable pus. A Foley "Y" plasty procedure was used here (fig. 5) with 42 days of splinting and drainage. It is the one case listed as a failure in which a good result was anticipated because there were no complicating factors. The reason for this poor result is not clear but possibly was due to the overly prolonged presence of foreign bodies (drainage tubes). A fourth patient has not had sufficient postoperative observation. Ultimately a good result has been obtained or is anticipated in 80 per cent of our cases.

#### SUMMARY

Twenty-three pyeloplastic procedures were performed by 8 operators on 20 patients whose average age was 27.2 years. There were no operative or postopera-

tive deaths. Most of these patients complained of chronic, repetitious, or acute pain in the lumbar area posteriorly, while in 4 cases anterior abdominal pain predominated. In one case, hematuria heralded the disease. The pathological change demonstrated most consistently was a congenital stenosis of the uppermost portion of the ureter. The operative procedure considered adaptable to most cases in this series was the Foley Y-V plasty. The urinary stream was diverted and the operative site splinted for a prolonged period of time in all cases. Infection was present in 9 cases preoperatively and it was evident in 11 cases on 3 months' follow-up. In 4 cases, calculi were present preoperatively and in two of these, they recurred postoperatively. In each the calculi were associated with infection.

#### OBSERVATIONS

Accurate diagnosis of ureteropelvic juncture obstructions is best made by an excretory urogram with delayed films and a retrograde ureteropyelogram with a 10 minute post injection "trapping" film.

The hydronephrotic kidney suitable for a pyeloplastic procedure is at present best determined by pyelograms, renal function tests, and the examination of the organ at the time of surgery.

The type of obstruction most commonly encountered in this series was congenital stenosis of the ureteropelvic juncture.

The Foley Y-V plasty was adaptable to the largest number of cases.

Diversion of the urinary stream and splinting of the ureteropelvic juncture for prolonged periods seem to be requisite.

Infection pre- or postoperatively did not obviate good results if good drainage was obtained.

The presence of infection plus calculi was attended by poor results.

Acid irrigations (Suby's solution) beginning at the first sign of a precipitate in the urinary drainage seemed to control adequately the problem of incrustation and calculus formation.

Corrective surgery of the ureteropelvic juncture should be performed only after significant objective findings have been demonstrated.

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## NONOPAQUE URINARY TRACT CALCULI

CHARLES C. HIGGINS

*From the Cleveland Clinic and the Frank E. Bunts Educational Institute, Cleveland, O.*

In recent years numerous articles have appeared in the literature considering the etiology of calculous disease, refinements in surgical technique and measures to be instituted to minimize the incidence of recurrent calculous formation.

The problem of nonopaque calculi has received but scant attention. The majority of statistics considering the relative opacity of urinary tract lithiasis were cited years ago before the introduction of modern equipment utilized in securing roentgenograms or before our familiarity with the chemical constituents of urinary tract calculi.

Urinary tract calculi may be subdivided into two groups.

- 1) The "pure calculi" are those in which only one crystalloid is present.
- 2) The "mixed calculi" in which two or more crystalloids enter into their composition.

True calculi are relatively rare as complete qualitative chemical analysis will usually reveal the presence of two or more salts. This was confirmed by Kleinschmidt who, in an analysis of apparently pure uric acid stones, detected traces of calcium carbonate, sodium and magnesium.

It is stated that "pure stones" are those which are composed of 95 per cent of one crystalloid. The purest calculi are uric acid, cystine and xanthine, or those in which excessive crystalloid excretion occurs in the presence of metabolic disease. Quantitative analysis of such calculi will reveal that 90 to 95 per cent of the total weight may be one salt. While pure oxalate stones are observed, other crystalloids such as uric acid and phosphates are frequently detected. Likewise uric acid stones may contain traces of xanthine. A pure phosphatic calculus is infrequently observed. Chemical analysis usually reveals the presence of ammonio-magnesium phosphate, calcium carbonate, calcium phosphate, and other salts in varying amounts. It has been my observation there is a definite increase in the incidence of pure and mixed oxalate calculi of the kidney in this country.

As might be anticipated, varying degrees of admixture of salts may be observed by quantitative and qualitative analysis from the so-called pure stone to the mixed type of calculus.

Mixed calculi may be subdivided into two groups.

1) In this type structural details indicate that precipitation of the different salts occurred simultaneously, resulting in the formation of a calculus in which the salts are diffusely and intimately mixed. This is the type of mixed calculus usually observed.

2) In this type of mixed calculus cross section of the stone will reveal the presence of lamination. This may be noted in a calculus composed of calcium oxalate, about which is a layer of calcium phosphate. In these instances the

Accepted for publication December 8, 1952.



part of the stone composed of calcium oxalate formed in the presence of sterile urine; with the introduction of a urea-splitting infection, the pH of the urine was shifted strongly to the alkaline side, enhancing the precipitation of phosphates, and thereby laying down a layer of phosphates around the oxalate calculus. The same phenomenon may be observed when a patient, having an oxalate calculus in the kidney, is placed on medication or a diet resulting in the production of an alkaline urine over an extended period of time. A layer of calcium phosphate may be deposited about a uric acid calculus due to similar circumstances.

The relative opacity of urinary calculi of equal diameters and thickness is determined by the atomic or the molecular weight of their constituents.

The opacity of a calculus is influenced by its size and depth, chemical constituents, and its structure.

The high incidence of visibility is due to the presence of calcium, a frequent constituent in the majority of stones.

In my experience the most opaque calculus is calcium oxalate, then calcium carbonate and, last, calcium phosphate.

The high relative opacity is due to the high atomic weight of the calcium present in these stones.

A lower relative opacity occurs in stones composed of uric acid, urates, cystine and xanthine or fibrin and bacterial concretions. It is generally stated that cystine renal calculi are nonopaque. While this is true for the small calculi, the larger cystine stones usually contain sufficient calcium to cast a shadow visible in the roentgenogram. This is substantiated by a review of the films of 13 patients harboring cystine renal calculi, all of which were well defined and radio-opaque.

Braasch and Emmett<sup>1</sup> state, "Most urinary calculi are sufficiently opaque to cast a shadow in the plain film. Opaque stones are usually composed of calcium oxalate, phosphate or carbonate. In a small percentage of cases stones may be nonopaque and incapable of casting a shadow. Nonopaque stones are usually composed of uric acid, urates, cystine, xanthine, or other organic material."

Since the pure type of calculus is less frequently observed than the mixed type, variations in the degree of opacity are inevitable.

#### RENAL CALCULI

Herman<sup>2</sup> states that approximately 5 per cent of renal calculi are not visible in the initial film. Young,<sup>3</sup> in a review of 184 cases of renal lithiasis, found that the roentgenogram disclosed the stone in 154 or 83.7 per cent. Joly<sup>4</sup> states that, in the properly prepared patient, renal stones may be visualized in 98 per cent

<sup>1</sup> Braasch, W. F. and Emmett, J. L.: *Clinical Urography*. Philadelphia: W. B. Saunders Co., 1915.

<sup>2</sup> Herman, L.: *The Practice of Urology*. Philadelphia: W. B. Saunders Co., 1938.

<sup>3</sup> Young, H. H. and Davis, D. M.: *Young's Practice of Urology*. Philadelphia: W. B. Saunders Co., 1926.

<sup>4</sup> Joly, J. S.: *Stone and Calculous Disease of the Urinary Organs*. St. Louis: C. R. Mosby Co., 1931

of the patients. He further stated that a calculus larger than a pin's head should cast a shadow in the radiogram unless composed of urates or uric acid.

Although the atomic weight of the constituents of a renal calculus may be such as to produce relatively low opacity, other factors may influence its visibility in a radiogram, namely:

The physical characteristics of the patient, the position of the kidney, the size of the calculus, the bowel contents, the immobilization of parts during exposure, and the technique of securing the radiogram.

The radiogram should show detail in the soft tissue comparable to the osseous detail of the ordinary radiograph. Mere outline of structure is not sufficient for a satisfactory film.

Fundamentally the clear delineation of the kidneys by radiography is based upon the difference in density between the kidneys and the surrounding tissues. Thus the presence of perinephric fat is of importance in clearly outlining the kidney. In patients with an abundance of perinephric fat, the outline of the kidney may be well defined, while in patients with but little perinephric fat, as in children, it may be difficult to secure a radiogram with a well defined renal outline.

The soft tissue technique for visualization of the kidneys and renal calculi is usually advisable. This will bring out the difference in density between stones of low opacity, the kidneys and the surrounding tissues.

The soft tissue radiograph is one which is made with the lowest voltage consistent with adequate penetration of the part examined. Milliampere second ratio is increased to give proper exposure, 200 to 300 milliampere seconds will usually give the best results.

In viewing the soft tissue radiograph, colored light such as red, green, and blue should be employed in addition to the usual white light. This may be readily accomplished by placing colored cellophane between the film and the illuminator. Shadows not discernible with the usual white light may stand out quite clearly with one of the colored lights. See figures 1 and 2.

In a stout muscular individual the calculus may cast a fainter shadow than usually observed, and, if the calculus has a relatively low opacity, only a faint shadow may be seen on the film. In this instance there is a greater thickness of tissue to be penetrated and the muscular tissue is more opaque than the perinephric fat. Thus a faintly opaque calculus may be difficult to visualize.

In instances in which the calculus is 1 to 2 mm. in diameter, it may usually be visualized by x-ray unless small and composed of uric acid, urates, cystine or xanthine, which may contain insufficient calcium to cast a shadow.

Fecal contents in the bowel may cast a mottled shadow of uneven density and obscure the faint shadow of a renal calculus, while gas in the bowel may have a similar action. Adequate preparation of the patient will eliminate this factor.

The majority of renal calculi cast a shadow of uniform density and the borders of the stone are well defined. In instances in which proper immobilization has not been secured during exposure, movement obviously occurs in the vertical

direction to the breathing of the patient. This is accompanied by blurring of the stone in its upper and lower edges, but the lateral borders remain well delineated. In such instances a calculus may be overlooked.

A stone with low opacity may not be visualized at times in the initial film in the presence of ptosed kidney or a congenital pelvic kidney. In the ptosed



FIG 1 A, nonopaque left renal calculus (cystine) B, nonopaque left renal calculus (uric acid)

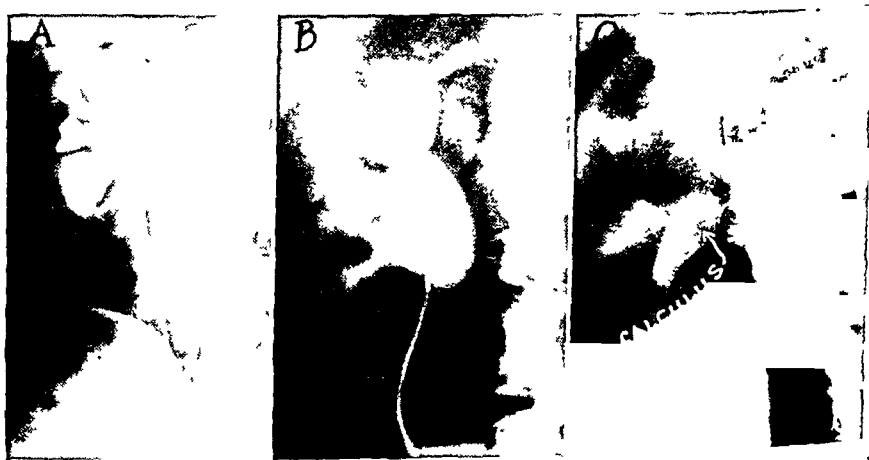


FIG 2 A, nonopaque right renal calculus (uric acid) B, nonopaque right renal calculus on lower calyx (cystine) C, nonopaque right renal calculus (uric acid)

kidney the stone may not be visible as it may overlap the shadow of the fourth lumbar vertebra, while in the pelvic kidney the bony structure of the pelvis may obscure the shadow cast by the renal stone of relatively low opacity.

It is evident that many calculi not discernible on the initial film are not in reality nonopaque stones, but numerous factors may influence their visibility, several of which have been enumerated.

#### URETERAL CALCULI

The shadow cast by a calculus in the ureter presents the same characteristics as that of a stone in the kidney. Again, the chemical composition influences the

roentgenographic findings. Oxalates cast the most dense shadows, next carbonates and, third, phosphates. A large ureteral calculus composed of cystine may be radio-opaque due to the calcium content of the calculus. Pure uric acid and urate ureteral stones are usually nonopaque.

Reports as to the roentgenologic visibility of ureteral stones show considerable variation. Statistics cited years ago related an incidence of 11 to 22 per cent in which the stone was not discernible.

Geraghty and Hinman<sup>5</sup> in 1915 were unable to demonstrate radiographically 15 of 67 cases of ureteral calculi, or 22.4 per cent. Braasch and Moore<sup>6</sup> in 1915 stated that radiograms gave negative results in 11 per cent. Herman<sup>2</sup> believed that 3 to 5 per cent of stones in the ureter were invisible. Israel,<sup>7</sup> in 1925, cited an incidence of nonopaque ureteral calculi of 1 to 4 per cent. Holmes and Peter-



FIG. 3. A, nonopaque left ureteral calculus (uric acid) B, nonopaque left ureteral calculus (uric acid).

son<sup>8</sup> observed, in a review of 100 cases of ureteral calculi, that 96 per cent were diagnosed by roentgenographic study.

In a review of our own last series of 500 consecutive cases of ureteral calculi 4 per cent did not cast a shadow or were overlooked in reviewing the roentgenogram.

Obviously statistics cited years ago are of little value, since modern equipment has greatly increased the percentage of ureteral calculi visible on stereoscopic films. See figure 3.

As in the case of renal calculi, although a ureteral stone may be radio-opaque, a negative diagnosis may be made. The extraneous factors such as physical characteristics of the patient, bowel contents, size of the calculus, and the position of the calculus in the ureter influence the visibility of the calculus.

<sup>5</sup> Geraghty, J. T. and Hinman, F., Ureteral calculi; special means of diagnosis and newer methods of intravesical treatment. *Surg., Gynec. & Obst.*, pp. 515-522, 1915.

<sup>6</sup> Braasch, W. F. and Moore, A. B., Stones in the ureter. *J. A. M. A.*, 65: 1234-1237, 1915.

<sup>7</sup> Israel, J. W., *Chirurgie der Niere und des Harnleiters*, p. 207, 1925.

<sup>8</sup> Peterson, H. O. and Holmes, G. W., Roentgen analysis of 100 cases of ureteral stone. *Am J Roentgenol.*, 37: 479-483, 1937.

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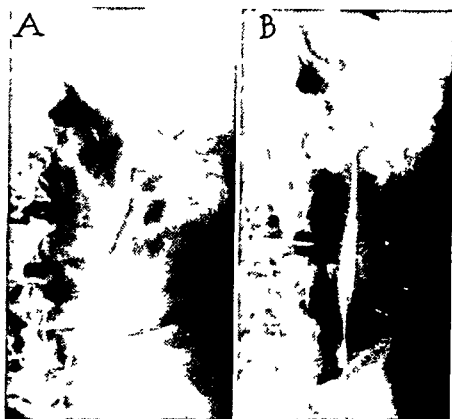


FIG. 1 A, nonopaque left renal calculus (cystine). B, nonopaque left renal calculus (uric acid).

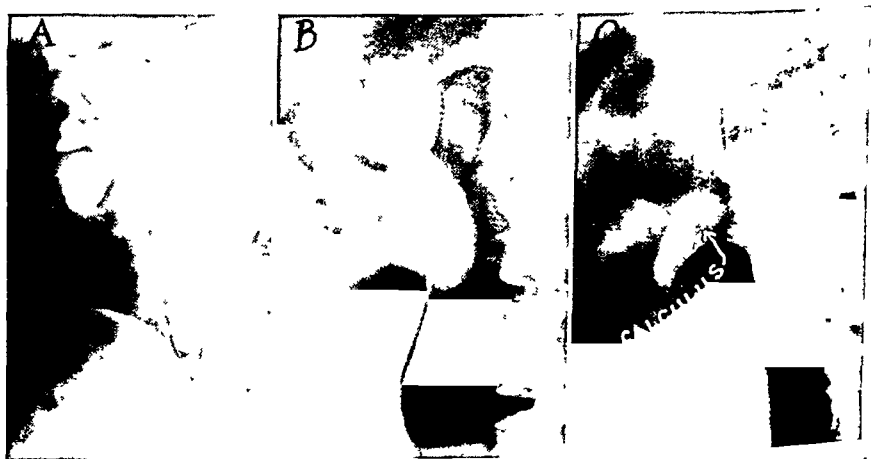


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It is usually stated that a ureteral calculus more than 2 to 3 mm. in diameter may be visualized unless composed of uric acid. To this I would add similar stones composed of urates, cystine and xanthine.

According to Peterson and Holmes,<sup>8</sup> the most frequently overlooked calculi are those located in a small area medial to the spine of the ischium and just above a line joining the lowest part of the ischial spines.

Likewise the stone shadow may be masked by the bony structure of the pelvis or overlooked because it is too small. The other factors influencing the visibility of ureteral stones have been discussed in relation to renal lithiasis.

#### VESICAL CALCULI

It has been stated that more than 50 per cent of stones in the bladder are not visible in the radiograms and in Hyman's<sup>9</sup> series 61 per cent were not disclosed. Nichols<sup>10</sup> stated that cystoscopic examination was the surest method for detecting vesical calculi, while, if the calculus or calculi were in diverticula, the roentgenogram furnished the most reliable procedure for their detection. Braasch and Emmett<sup>1</sup> state that of all urinary calculi, those situated in the urinary bladder are most often overlooked when one is examining the plain film. They further state that, even when the roentgenograms are most carefully studied, a large percentage of vesical calculi will be missed.

Joly<sup>4</sup> has said that, due to the fact that a large number of vesical calculi are composed of uric acid which is transparent in x-rays, radiography is by no means as accurate in the diagnosis of stones in the bladder as it is in cases where the calculus occupies a position in the upper urinary tract. He concludes that, in a patient with symptoms suggestive of a vesical calculus, a negative x-ray examination would never be accepted as conclusive. A cystoscopic examination should always be performed to confirm the radiographic findings.

It is well to recall that many stones in the bladder designated as "nonopaque" are not in reality transparent. Such stones, frequently phosphatic in type, have the same relative opacity as the soft tissues in the body and therefore are not visible on the radiogram. Also, the shadow cast by the calculus frequently lies over the sacrum, obscuring the stone in the x-ray film. Fecal contents in the inadequately prepared patient may likewise obscure the faint shadow of a vesical calculus.

I agree that the percentage of error in establishing the diagnosis by roentgenography is sufficiently great to make a cystoscopic survey advisable in all cases suspected of vesical calculus.

It is obvious, therefore, that the term *nonopaque stone*, as applied to calculus disease of the urinary tract, is not strictly accurate and has been used rather unscientifically. Many stones which are, in reality, *radio-opaque*, are not discernible in the radiogram due to extraneous factors, or incorrect application of sound radiographic procedures.

<sup>9</sup> Hyman: cited by Higgins.

<sup>10</sup> Nichols, B. H. and Lower, W. E.: *Roentgenographic studies of the urinary system*. St. Louis: C. R. Mosby Co., 1933.

## ROENTGEN DIAGNOSIS

A stereoscopic radiogram should be secured routinely in a patient with symptoms suggestive of calculous disease, as the information elicited is more accurate than that obtained by a simple radiogram. All such radiograms should be secured with the Bucky diaphragm and the cassettes should have satisfactory intensifying screens.

An excretory urogram will frequently disclose the presence of a stone in the kidney which is radio-opaque, or of relatively low opacity, which would be obscured by the retrograde urographic media, the filling defect having the characteristic features of a renal calculus.

Occasionally, however, after the ureteral catheter has been removed following retrograde pyelography, a delayed film secured an hour later reveals sufficient medium adherent to the nonopaque stone to render it radio-opaque. I have no hesitation in performing an air pyelogram when nonopaque renal calculi are suspected, and as yet have observed no untoward results.

The excretory urogram, or retrograde pyelo-ureterogram may disclose filling defects in the ureter in the presence of nonopaque ureteral calculi, and at other times the stone may be visualized by an air pyelo-ureterogram. It is the general opinion, with which I concur, that roentgenography should not be relied upon to establish the diagnosis of vesical calculi. In patients with symptoms suggestive of vesical lithiasis cystoscopy is always advisable.

Sins of omission are usually responsible for overlooking nonopaque calculi in the urinary tract. The subsidence of the pain following an attack of colic in the presence of a normal, initial film often leads to the erroneous deduction that the stone was expelled spontaneously or that the discomfort was due to the passing of a shower of crystals. Nonopaque stones in the urinary tract undoubtedly occur more frequently than we are led to presume from a review of the literature.

## CONCLUSIONS

The term "nonopaque stone" frequently is scientifically unsound, and is applied to calculi of relatively low opacity.

Extraneous factors influence the opacity of calculi discernible on the radiogram.

True nonopaque stones in the kidney and ureter are relatively uncommon.

Faintly opaque calculi not discernible on the radiogram due to extraneous influencing factors occur more frequently than we are led to believe from reports in the literature.



## NEUROBLASTOMA IN A CASE OF HORSESHOE KIDNEY

J. M. TAYLOR, P. E. RUSSO AND M. E. JACOBSON

*From the Departments of Urology and Radiology, University of Oklahoma, School of Medicine, University Hospital, Oklahoma City, Okla.*

The following case is presented because of the interesting combination of a congenital anomaly associated with a relatively rare type of abdominal tumor. Although no exhaustive search of the literature was made, we found no reports of an abdominal neuroblastoma associated with a horseshoe kidney. A case of a horseshoe kidney associated with a Wilms's tumor was reported by Eliason in 1944 and another by Nathan Smith in 1946. The incidence of horseshoe kidney has, by various observers, been estimated to occur from 1:200 to 1:468 cases. D. K. Rose reported a case of Wilms's tumor in the isthmus of a horseshoe kidney in 1945.

### CASE REPORT

G. S., No. 176-272, a 2 year old white boy, was admitted to the University Hospital September 21, 1951. The present illness began 2 weeks prior to admission when the patient fell to the ground. After this incident he complained of abdominal pain and vomited in a few hours. The following day the patient became lethargic and had a high temperature. The local physician informed the patient's mother that the baby had an abdominal tumor. The patient continued to have fever, anorexia and abdominal discomfort until his admission to this hospital 2 weeks later. No other details of present or past history were of any significance.

Temperature 101.2F, pulse 112, weight 26 pounds, height 32 inches. The patient appeared to be chronically ill, rather irritable and pale. Examination of the head, neck and chest were negative. Inspection and palpation of the abdomen revealed a firm, fixed tumor mass occupying the entire left abdomen, extending slightly across the midline. The mass was approximately 15 by 20 cm., easily palpable, did not move with respiration, and was thought to be retroperitoneal. Physical examination, otherwise, was not remarkable.

Laboratory data: Red blood cells 3,060,000, hemoglobin 8 gm., white blood cells 15,250 with a normal differential count; nonprotein nitrogen 22 mg. per cent, CO<sub>2</sub> combining power 67.2 volumes per cent, chloride 102 mEq., urine was cloudy, pH 5.5, protein and glucose negative, white blood cells 2-4 per high power field, much mucus.

Radiographic examination of the chest revealed no abnormalities of heart, lungs, mediastinum or bony thorax. Films of the long bones, spine and pelvis revealed no abnormalities of the bones or joints. A plain urogram showed a soft tissue mass located in the left upper abdomen extending beyond the midline to the right side. Excretory urograms indicated good excretory function of both kidneys. The right kidney was rotated on its long axis so that the pelvis and ureter were located on the lateral aspect of the kidney. The left kidney was visualized and

Accepted for publication November 25, 1952.

located also on the right side, below the right kidney. The left ureter was seen to cross over to the left side to enter the urinary bladder in its normal position (fig. 1, *A*). Retrograde pyelograms 3 days later confirmed our previous impression that both kidneys were located on the right side (fig. 1, *B*).

We were certain that we were dealing with a large retroperitoneal tumor and fused kidneys, but it was not clear whether the retroperitoneal tumor, because of its large size, had displaced the horseshoe kidney from the left side or whether it was associated with the rare anomaly of crossed ectopic kidney.

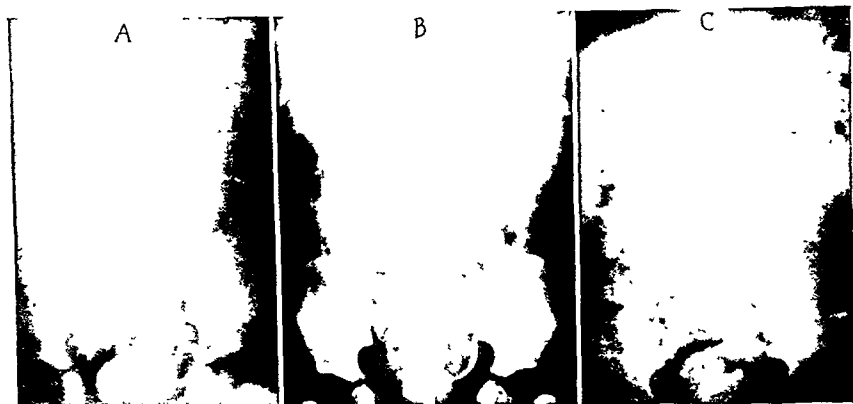


FIG. 1. *A*, excretory urogram shows rotation of right kidney on its long axis. Left kidney displaced to right iliac area by large retroperitoneal tumor on left side. Left ureter crosses midline from right to enter urinary bladder on its left side. *B*, retrograde pyelo-ureterogram shows both kidneys on right with a crossed ectopic ureter on left. At surgery it was proved to be horseshoe kidney displaced by large left retroperitoneal tumor. *C*, excretory urograms following surgery. Left kidney has resumed its normal position to left of lumbar spine. Configuration of horseshoe kidney is now more apparent.

The patient was explored on the sixth hospital day through a left rectus abdominal incision. The retroperitoneal tumor was found to be well encapsulated and attached to the convex border of the left kidney and to the tissues in the left dorsal peritoneal space. These attachments required sharp dissection and numerous ligatures to control the bleeding. This large tumor had displaced what was now proven to be a horseshoe kidney. The immediate recovery from this operation was satisfactory.

Examination of the gross specimen showed that the tumor was soft, friable and dark red in color. The capsule was thin and ruptured at its several points of attachment. Microscopic examination shows nests and sheets of small, deeply staining round cells composing most of the tumor. No definite rosette or pseudo-rosette formation was demonstrated but there was a tendency towards paravascular rimming by tumor cells. Microscopic diagnosis: Neuroblastoma (fig. 2, *A*). A specimen obtained from the liver at a later date showed similar cellular structures as the primary tumor (fig. 2, *B*).

Following surgery excretory urograms showed that the left kidney was located to the left of the lumbar spine. The configuration of the horseshoe kidney became easily apparent (fig. 1, *C*).

Deep x-ray therapy was started on the eleventh postoperative day and was completed 1 month later. A rest period of 2 weeks was necessary during this series of treatments because of severe radiation sickness and the debilitated condition of the patient. A dose of 1000 r, measured in air, was delivered to an anterior and posterior field over the left renal area using 200 KV 2 mm. Cu + 1 mm. Al, 50 cm. distance and a field of 15 by 15 cm. and a daily dose of 150 r. A radiographic skeletal survey repeated at this time again failed to reveal any metastatic lesions.

The postoperative course was complicated by irregular, moderate elevations of temperature with periods of remission and slow wound healing characterized by local induration and serous drainage. However, during most of this period

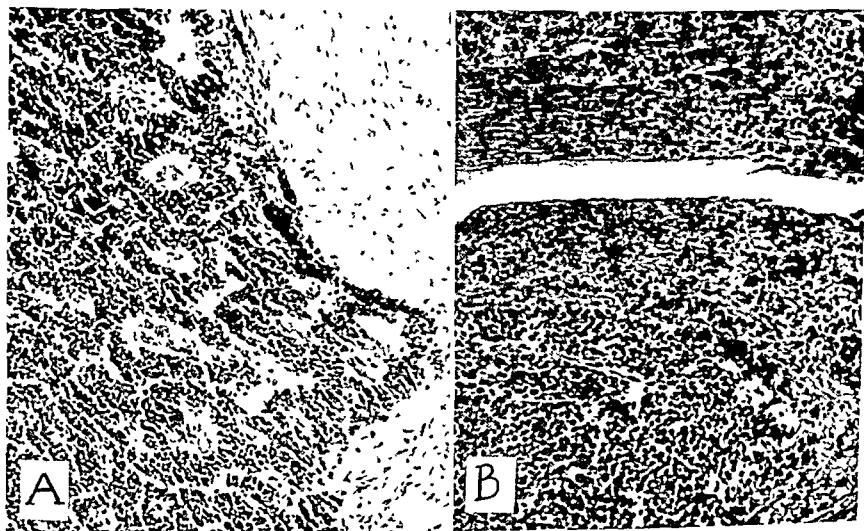


FIG. 2. A, portion of primary tumor. Nests and sheets of small deeply staining round cells compose most of tumor. No definite rosette or pseudorosette formation is demonstrated but there is a tendency toward paravascular rimming by tumor cells. B, metastatic deposits of tumor within liver composed of cell same appearance as in primary tumor.

the patient was up and around in the crib and presented a fairly normal appearance. On discharge 90 days postoperatively his weight was only 2 pounds less than on admission.

The patient was re-admitted January 7, 1952 with a history of failing appetite, lethargy and an increasing enlargement of the abdomen. Examination revealed an acutely ill patient with dyspnea, decreased breath sounds at both bases and marked ascites (500 cc of bloody fluid obtained at paracentesis). The patient expired 10 days after the second admission.

An autopsy was obtained and the following final diagnoses were made: 1) Neuroblastoma, retroperitoneal, left, recurrent with extensive metastases to all organs of the abdominal cavity and to pleural cavities and to lungs with pleural effusion; 2) subphrenic abscess, massive, chronic, left; 3) cachexia; 4) congenital horseshoe kidney with re-duplication of left ureter and extra-ureteral orifice in prostatic urethra.

## DISCUSSION

Lewis and Papez noted that the renal anlage in 10-12 mm. pig embryos lay in close proximity in the crotch formed by the umbilical arteries and might well come in contact and fuse at this point during the ascent of the kidneys. In certain other cases renal fusion might result from growth of both ureters into a common renal blastema. It is most likely that the fusion explains the failure of the horseshoe kidney pelves to rotate into their normal mesial position. Farman stated that the isthmus in 85 per cent of the cases is made up of kidney parenchyma and of fibrous tissue in 15 per cent.

Lewis's *System of Surgery* defines neuroblastoma as a highly malignant tumor, arising from the undifferentiated cells of the primordium of the autonomic and chromaffin system. The cells are derived from the neuroblast and the undifferentiated parent cell. According to Weisel, evolution of the suprarenal medulla may be prolonged beyond puberty and may contain undifferentiated neuroblasts even in the second decade of life; although rarely do these cells persist after the first few weeks of intrauterine life. Malignant neuroblastoma cells may go on to mature into non-malignant cells in the early years of life. Cases have been reported where apparently originally malignant neuroblastomas, with metastases to other organs, have been removed and were found to be differentiated and benign tumors that had matured, i.e., in the original tumor. Hence neuroblastomas have some capacity for spontaneous loss of malignancy. There is some question whether these cases may be truly metastases or abnormal embryonal rests of neuroblastic tissue. Cases of spontaneous maturation of these tumors into benign ganglioneuroma following biopsy have been reported. Occasionally hemorrhage into the tumor results in its disappearance.

Neuroblastomas show a predilection to occur in the suprarenal but may also be primary from undifferentiated neuroblasts in the cervical or lumbar sympathetic ganglia, spinal cord, retina, kidney, Meissner and Auerbach's plexus of the small intestine, nasal cavity, uterus and bladder neck. In the suprarenal type, as noted in this case, the kidney is usually not involved. As our films indicate, the horseshoe kidney in this case was displaced downward and mesially in the pattern of a crossed ectopia.

In any large tumor palpable in the abdomen of a child, which presumably is retroperitoneal, the very great majority will be found to be Wilms's tumor or neuroblastoma. According to Pilcher, neuroblastoma is about one-half as frequent as Wilms's tumor. The former tends to occur earlier in life. Wells, in 1940, reported 17 cases of neuroblastoma of the adrenal present in infants at birth. Neuroblastoma is especially to be considered in an abdominal tumor in children under the age of four. In 64 cases of malignancy under 13 years of age, reported by Scotti in 1939, 30 per cent were due to Wilms's tumor and 10 per cent to neuroblastoma. Malignant tumors in children, under the age of 8, are the most common in the kidney or adrenal (Kellert).

Wittenberg summarized the result of treatment in 73 cases of neuroblastoma, stating that 20 patients are still alive, after 12-16 years. Surgery and postopera-

tive x-radiation gave the best prognosis; although, there are cases reported in the series that survived 3 years or more with only x-ray therapy.

#### CONCLUSION

We have reported a case of neuroblastoma in a child which was associated with a horseshoe kidney. The retroperitoneal tumor became so large that it displaced the kidney on that side to the opposite side of the abdomen. After surgical removal of the tumor the kidney assumed its proper position and proved that we were not dealing with a crossed ectopic kidney but with a horseshoe kidney.

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## HEMANGIOMA OF THE KIDNEY PELVIS

JOSEPH B. ANDERSON, JAMES J. LEE, REGINALD A. HANCOCK AND  
SAMUEL R. BLACK

Hemangioma or angioma of the kidney is an uncommon finding. The first authentic case was found at autopsy by Virchow in 1867. Riley and Swann<sup>1</sup> in 1941, after a review of the literature, were able to find only 36 cases. They added one case which they had observed. Mayo Clinic<sup>2, 3</sup> through August 1944 reported only 2 cases of hemangioma of the kidney. Boston City Hospital, January 1, 1939, did not find one case of renal hemangioma in 13,219 autopsies. Bell<sup>4</sup> found one case in 30,000 necropsies. Prior to September 1947, Roff and Podolsky<sup>5</sup> found 68 instances of renal hemangioma reported in the literature; of these cases only 11 occurred in the kidney pelvis. They added one case which they had observed. In September 1947, Lazarus and Marks,<sup>6</sup> after a very extensive and exhaustive review of the literature, analyzed 70 cases of renal hemangioma; this total included one case of their own.

### CASE REPORT

Mrs. L. R., aged 47 years, was seen September 8, 1951, for a persistent painless hematuria of 24 hours' duration. There was no history of frequency, nocturia, burning or night sweats. She had lost 18 pounds in the past 4 weeks.

This patient had been seen 14 years previously, September 22, 1937, for a similar complaint: painless hematuria of 6 days' duration.

At that time, cystoscopic examination revealed a slightly inflamed bladder. The urine from the right ureteral orifice was smoky while that from the left orifice was clear. Indigo carmine intravenously appeared from both kidneys in 3 minutes and concentrated in 5 minutes after injection. X-ray and bilateral pyelograms did not reveal any filling defects or opaque urinary calculus.

The patient returned 18 days later at which time her hematuria had subsided. She was not seen again until the onset of her present illness.

She had an appendectomy in 1934.

Cystoscopic examination (September 1951): The bladder urine was grossly bloody with a few small clots. The bladder mucosa was normal in appearance and did not show any evidence of ulcer, tumor or recent hemorrhage. There was a bloody efflux from the right ureteral orifice while clear urine appeared from the left orifice. Both ureters were catheterized without encountering any obstruction. No residual urine was obtained from either kidney pelvis. Indigo carmine, intravenously, appeared from the left kidney in 3 minutes, and concentrated in 5 minutes. Some dye appeared from the right kidney but because of the blood, an accurate estimate could not be made.

Accepted for publication December 8, 1952.

<sup>1</sup> Riley, A. and Swann, W. J., Jr.: *Urol. & Cutan. Rev.* 45: 377-382, 1941.

<sup>2</sup> Judd, E. S. and Simon, H. E.: *Surg. Gynec. & Obst.*, 46: 711, 1928.

<sup>3</sup> Rives, H. F. and Pool, T. L.: *J.A.M.A.* 125: 1187, 1944.

<sup>4</sup> Bell, E. T.: *J. Urol.* 39: 238, 1938.

<sup>5</sup> Roff, L. G. and Podolsky: *N. Y. State J. Med.* 51: 1536, 1951.

<sup>6</sup> Lazarus, J. A. and Marks, M. S.: *Urol. & Cutan. Rev.*, 51: 500-509, 1947.

X-ray with catheters in situ was negative for any shadows suggestive of opaque urinary calculus.

The right pyelo-ureterogram showed a filling defect in the upper calyx (fig. 1). The ureter was normal. The left pyelo-ureterogram was normal.

Because of the possibility of the filling defect being due to blood clot, the patient was given vitamin K, and asked to return for further study. Ten days later, the findings were the same. The hematuria had continued during this period.



FIG. 1. Pyelogram demonstrating filling defect in upper portion of right kidney pelvis (Right pyelogram 10 days later showed same defect)

A diagnosis of tumor or non-opaque calculus in the right kidney pelvis was made.

The patient was admitted to the hospital September 23, 1951.

The patient did not appear acutely ill. The eyes showed a suggestive exophthalmus. The thyroid gland, especially the left lobe, was enlarged. Heart and lungs were negative. Blood pressure was 180/70 and the pulse was 96 per minute. There was no tenderness in either costovertebral angle, and neither kidney was palpable. Reflexes were hypertonic.

X-ray of the chest was negative for metastases.

Catheterized urine was brown in color; acid; specific gravity 1.012; albumin 4 plus; sugar, negative. Microscopic: many red blood cells and moderate amount of bacteria.

Blood chemistry: Glucose 80 mg. per cent; urea nitrogen 9.7 per cent. Blood

count: Red blood cells, 3,820,000; white blood cells, 5,100; hemaglobin 77.8 per cent (12.0 gm.). Differential: Neutrophils, 63 per cent; lymphocytes, 34 per cent; monocytes, 3 per cent. Blood type: Group O Rh +.

Operation (J. B. A., September 25, 1951): Under spinal pentothal anesthesia, the right kidney was exposed through a curved right lumbar incision. The kidney was normal in shape, size and appearance. Palpation of the pelvis did not reveal any tumor or stone. Despite that fact and because of the persistent hematuria and pyelographic changes, a right nephro-ureterectomy was performed. The procedure was carried out in the usual manner without difficulty except for marked adhesions around the lower portion of the ureter. The kidney and ureter were removed intact through a modified right Gibson incision. A Penrose drain was placed in the kidney fossa and brought out through the lumbar incision. The Penrose drain in the right post-vesical space was brought out through the lower incision. A retention catheter was placed in the bladder at the close of the operation for continuous drainage. The patient received 500 cc of blood during the procedure.

On the second postoperative day, she became markedly distended and complained of severe gas pains. This was relieved by copious bowel movement on the third day. The drains and sutures were removed by the sixth postoperative day, and the drainage decreased markedly. On the eighth day, there was an excessive amount of dark brown drainage but no clots from the lumbar incision. The incision was packed daily, and the drainage subsided by the seventeenth postoperative day.

The patient was given a transfusion of 500 cc of blood on the thirteenth postoperative day, and she was discharged on the nineteenth postoperative day.

Six weeks later the incisions were well healed; catheterized specimen of urine was negative chemically and microscopically, and she had regained some of her weight loss.

The gross specimen consisted of the right kidney and included 27 cm. of ureter. The kidney weighed 155.01 gm. It was normal in shape. The capsule was easily stripped. The surface was smooth and purplish tan. Upon sectioning, the cortex was pale, brownish purple and glossy. The markings were distinct. In the medulla, there were numerous patches of intense hyperemia and linear reddish purple areas. The papillae were pale, glistening and smooth. The major and minor calyces were structurally intact. There was no deformity of the renal pelvis. The mucosa of the pelvis was mottled with bright red and dark purple red hemorrhagic patches. Two soft mushy brownish and reddish purple masses measuring approximately 4.0 mm. in diameter were found in the lumen of the pelvis. In an area of the pelvis, just beneath a papilla, there was a 2.0 mm. in diameter hemorrhagic bleb.

The mucosa of the ureter was silvery and smooth. Its lumen was of normal caliber. In the midcortical region a 1.0 mm. in diameter bluish area was observed.

Microscopic description (fig. 2): The purplish blebs in the pelvis, just beneath one of the papillae, consisted of large vascular sinuses lined by endothelium filled with red blood cells and occasionally by thrombi. The hemangiomatous



tumor was quite extensive and was divided by broad bands of stroma into several portions extending for a short distance into the medulla. In some areas, the lesion had a telangiectatic structure but, for the most part, the vessels were large and tortuous. The largest of these had eroded the overlying pelvic epithelium and bulged above the surface. The stroma about the tumor was diffusely hemorrhagic and edematous. Varying numbers of lymphocytes had infiltrated the stroma about the tumor. Throughout the kidney substance, there were fairly numerous scattered interstitial hemorrhages. The glomeruli, for the



FIG. 2. High power photomicrograph demonstrating area of hemangioma with erosion into kidney pelvis.

most part, were well preserved. Here and there the tubules were dilated and contained yellowish brown cast. The medium size and small arteries exhibited moderate degrees of hyaline fibrosis of their walls with reduction in the caliber of their lumens. Diagnosis: Cavernous hemangioma of the right renal pelvis with erosion of the pelvic mucosa and hemorrhage into the pelvic cavity.

Rarely is the diagnosis of renal hemangioma possible before the kidney is removed. The most common and sometimes the only symptom is hematuria; this is usually intermittent but may be persistent. In the case reported by Roffand Podolsky, hematuria was absent. The passage of blood clots down the ureter often produces renal colic. Hemorrhage may be so profuse that immediate operation is necessary. According to Hamm<sup>7</sup> in 85 per cent of the cases studied

<sup>7</sup> Hamm, F. C.: J. Urol., 55: 143, 5946.

by Riley, and Swann, the onset of hematuria occurred in patients under 40 years of age. The presence of a tumor mass or costovertebral angle tenderness is usually not elicited. Bladder symptoms are rare. Pyelographic studies may reveal the type of filling defect, usually seen in neoplastic disease. It must be borne in mind that blood clots, non-opaque calculus, or cyst may give rise to similar defects.

#### DISCUSSION

This disease usually occurs in patients under 40 years of age; the youngest reported case was 4 days old, and the oldest 66 years of age. The left kidney is involved slightly more than the right; a few more cases have been reported in men than women. It may occur with or without pain. The bleeding may be persistent or intermittent, slight or profuse, and may be present from a few days to as long as 36 years. Pyelographic changes, when present, are similar to those usually seen in renal neoplasm, tuberculosis or nonopaque calculus.

This disease is unilateral and the lesion may vary in size from a pinpoint, usually located in a papilla, to a mass occupying one-third of the kidney. Hemangioma is considered a true neoplasm rather than a dilatation of existing blood vessels. Cases of so-called essential hematuria, especially if unilateral, should be repeatedly investigated pyelographically, especially if the initial pyelograms are normal. Only in this way can the lesion be diagnosed correctly.

The persistent or excessive loss of blood caused by these tumors frequently necessitates nephrectomy. Some cures have been reported by less radical procedures. Recovery after operation is to be expected.

Since the disease is unilateral, nephrectomy is the treatment of choice in the majority of cases because hematuria is usually excessive or persistent.

#### SUMMARY

Hemangioma of the kidney is a rare benign tumor. This disease is of interest, however, since it may account for some instances of obscure renal bleeding. Hemangioma may be located in any part of the kidney but will cause hematuria only when connected with the renal pelvis.

Although only 70 cases of renal hemangioma have been reported, these tumors are probably more common than this figure would indicate.

Hemangioma of the kidney is unilateral and benign; recovery after operation is to be expected.

*501 Jenkins Bldg., Pittsburgh 22, Pa.*

## URETERAL ELECTROMYOGRAPHY

ROGER BAKER AND JOHN HUFFER

*From the Department of Surgery (Division of Urology), The University of Chicago, Chicago, Ill.*

It has been demonstrated in recent years that electromyography is a recognized clinical procedure. Experimental techniques for recording electrical responses of muscles can be utilized for quantitative measurement of functional impairment in man resulting from lesions in the central nervous system, peripheral nerve injuries and disorders affecting the neuromuscular junction. It is obvious that electromyography can be used only on the basis of deviation from the known normal patterns of muscular activity. At present little is known concerning electromyography of the ureter. No standard electrical patterns are available of normal, intact, ureteral muscular activity. The purposes of this paper are to present an experimental investigation of ureteral action potentials in the normal dog. These results will then be compared with electro-ureterograms obtained after re-anastomosis of the divided ureter to bladder, uretero-intestinal implantation, and incomplete occlusion of the ureter. A subsequent communication will report ureteral electrical activity in patients with congenital megalo-ureter.

The smooth muscles of the ureter have a double nerve supply; the sympathetic innervation decreases, while the parasympathetic increases, ureteral motility. The ureteral nerve supply is not indispensable for contraction though capable of causing and modifying it. Engelmann observed that the excised ureter requires no extrinsic nerves for contraction. The ureteral smooth muscles are composed of fusiform cells connected together by fine intercellular bridges to form a syncytium, by which, in all probability, the excitatory process can be transmitted from cell to cell. Bozler investigated the effects of this type structure and observed that a stimulus applied to any level of the ureter caused a wave of excitation to proceed in both directions away from the stimulus. It is well known that the ureteral smooth muscle is very sensitive to mechanical stimuli. Distention of the ureter with urine causes contraction. Using an excised kidney-ureter preparation, Hryntschak demonstrated that dye injected into the renal pelvis passed down to the ureter by peristaltic action. In 1911 von Brücke and Orbeli reported that peristalsis in the ureter of the normal dog, rabbit, and guinea pig is associated with a triphasic action potential. Other investigators have reported experimental bioelectric studies of the ureter that are not referable or directly applicable to clinical problems.

### PROCEDURE

*Technique.* All experimental surgery was performed on healthy adult male or female mongrel dogs while observing usual aseptic precautions. Except where indicated, no effort was made to control preliminary hydration. Preoperative

This work was supported in part by an American Cancer Society Institutional grant, The United States Public Health Service and the Gerber Memorial Cancer League.  
Read before the Chicago Urological Society, December 11, 1952.

medication consisted of atropine and morphine sulfate, and the anesthetic agent used was intravenous sodium seconal, 30 mg. kg., or ether.



FIG. 1. Method used to obtain electro-ureterograms. Ureter isolated for 2-4 cm. and lifted off underlying muscle by glass hook. No. 28 hypodermic needle attached to insulated wire inserted into muscularis of ureter.

## Unipolar Electro ureterograms

Tracings I through IV are of the same ureteral action potentials.

Filters have been inserted stepwise to eliminate cycles of slow frequency.

Tracing I includes all slow and fast frequency cycles, while IV includes the least amount of slow frequency cycles

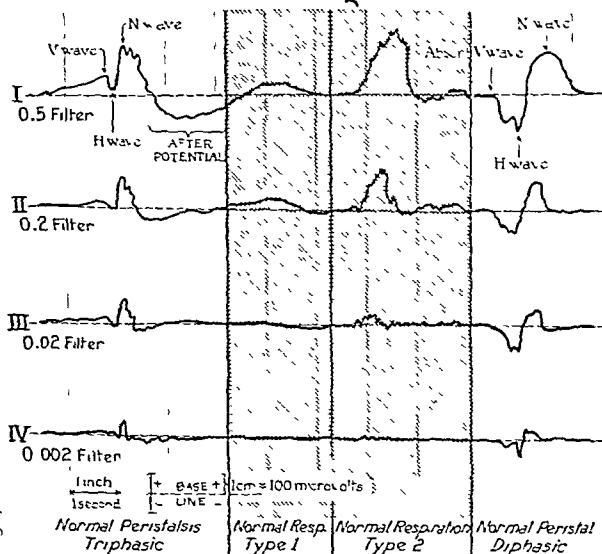


FIG. 2. Demonstration of channels and calibrations used in obtaining unipolar electro-ureterograms

Laparotomy was performed and 2-4 cm. of the ureter was carefully freed of peritoneum, anteriorly, and the underlying muscle, posteriorly. A small glass hook was used to gently elevate the ureter from the underlying muscle. The glass rod was suspended between two ring stands, one on either side of the dog. An active electrode, consisting of a number 28 hypodermic needle, 1 cm. in

length and attached to an insulated wire, was inserted in the suspended ureter (fig. 1). A neutral or "indifferent" electrode was placed in the skin of the abdomen and the dog was grounded by a contact attached to a hind leg. Electrical impulses passing down the ureter were obtained and amplified by means of a standard Offner electro-encephalographic machine and were recorded by a crystallographic ink-writing unit.

*Calibration.* The shape of the electro-ureterogram recorded was the result of change in frequency and amplitude (voltage). Duration was expressed in milliseconds. Amplitude was calibrated at 100 mv/cm. above (positive) or below (negative) the base line. Determination of frequency of peristalsis was constant

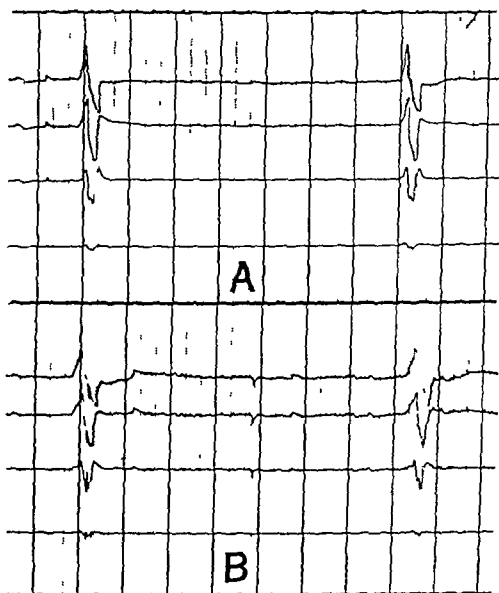


FIG. 3. *A*, normal diphasic peristaltic action potentials in intact ureter. *B*, same ureter transected distal to insertion of electrode. No alteration in peristaltic electrical activity.

for each experiment as the graph paper moved beneath the recording pens at a rate of 2.5 cm./second. Each experimental tracing usually had four channels in which various filters were inserted to progressively remove slow frequency cycles: channel one, 0.5 filter; channel two, 0.2 filter; channel three, 0.02 filter and channel four a 0.002 filter. Channel four had the least number of slow frequency cycles. All statistical data was obtained from channel one, using a 0.5 filter (fig. 2).

## RESULTS

*I. The normal electro-ureterogram.* Despite minor variations, normal peristalsis is usually qualitatively characterized by a triphasic action potential. Only four of the 23 ureters studied were diphasic in form. Triphasic waves always consisted of two positive waves separated by a negative wave that usually did not reach the base line (figs. 5, *A*, 6, *A*). Diphasic curves had a positive wave followed by a negative wave of inconsistent voltage and duration (fig. 3, *A*).

After-potential curves were observed in only three tracings of the normal intact ureter. Data concerning voltage and duration of representative normal triphasic electro-ureterograms are presented in tables 1 and 2.

Factors affecting the normal electro-ureterogram: 1) Preoperative medication and anesthetic agent: Regardless of whether large doses of morphine and atro-

TABLE 1. *Amplitude\* of normal triphasic ureteral peristaltic action potentials*

| DOG            | WAVE 1     | WAVE 2     | WAVE 3     |
|----------------|------------|------------|------------|
| 372            | 20         | 110        | 330        |
|                | 220        | 200        | 170        |
| 22             | 150        | 160        | 250        |
| 131            | 180        | 120        | 200        |
|                | 200        | 140        | 90         |
| 345            | 160        | 180        | 80         |
| 227            | 90         | 120        | 130        |
| 346            | 70         | 40         | 140        |
| 183            | 150        | 190        | 160        |
| Range          | 20-200     | 40-200     | 80-330     |
| Mean and S.D.† | 138 ± 20.5 | 140 ± 20.7 | 172 ± 25.1 |

\* Microvolts.

† Standard Deviation.

TABLE 2. *Duration\* of normal triphasic ureteral peristaltic action potentials*

| DOG            | WAVE 1    | WAVE 2    | WAVE 3    | TOTAL TIME |
|----------------|-----------|-----------|-----------|------------|
| 372            | 16        | 44        | 44        | 104        |
|                | 20        | 40        | 24        | 84         |
| 375            | 24        | 12        | 72        | 108        |
| 22             | 26        | 20        | 32        | 72         |
| 131            | 40        | 4         | 52        | 96         |
|                | 32        | 24        | 44        | 100        |
| 345            | 36        | 24        | 20        | 80         |
| 227            | 56        | 24        | 32        | 112        |
| Range          | 16-56     | 4-44      | 20-72     | 72-112     |
| Mean and S.D.† | 31 ± 13.1 | 24 ± 13.2 | 40 ± 16.8 | 95 ± 12.3  |

\* Milliseconds

† Standard Deviation.

pine were administered or not given at all preoperatively, or whether ether or intravenous sodium seconal were used as anesthetic drugs, the same qualitative and quantitative characteristics of each of the peristaltic action potentials were observed.

2) Local conditions of ureter. If the segment of the ureter containing the needle electrode touched the underlying muscle or adjacent bowel, the electrical tracings were contaminated with superimposed artifacts, often with electrocardiograms.

3) Hydration: It is well known that dehydration or increased hydration of the dog produces a decrease or increase, respectively, in renal urinary output and also affects the rate of peristalsis per unit time. Atropine, chilling of the ureter, and drying out of the ureter may also produce a change in rate of peristalsis. To demonstrate this phenomenon is extraneous to the purpose of this communication. In the present experiment it is reported that these factors failed to significantly alter the qualitative or quantitative pattern of the individual peristaltic action potentials.

4) Motion artifacts: Motion of the ureter, glass hook or suspension apparatus created motion artifacts that rendered interpretation of peristaltic action potentials impossible.

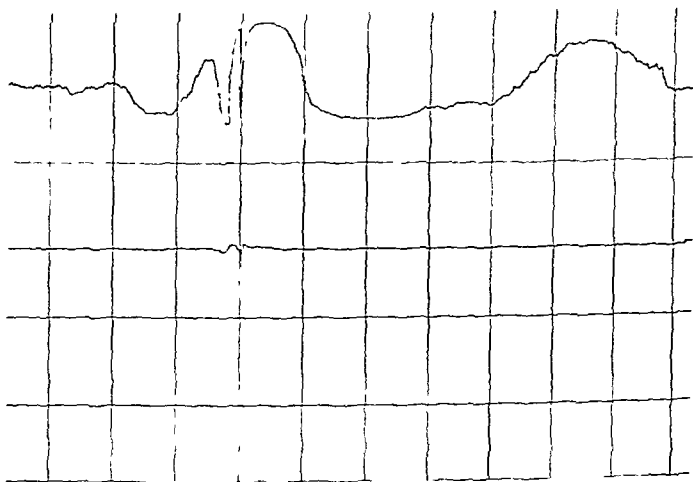


FIG. 4. Normal triphasic peristaltic action potentials. Notched third curve. This peristalsis was not observed grossly, but spurt of urine emerged from cut ureter and above electrical pattern indicative of peristalsis was recorded. This was not uncommon finding.

*II. Immediate results after ureteral transection.* Of the 18 ureters studied, transection routinely produced no significant alteration in voltage or duration when compared to normal peristaltic action potentials (fig. 3). Dividing the ureter may produce one, and frequently two, after-potentials immediately following the peristaltic curve.

*III. Delayed results after transection of the ureter and re-anastomosis to bladder or uretero-intestinal implantation.* Eight transected ureters were re-anastomosed to the bladder and an equal number were implanted in the bowel. As there was no significant difference in ureteral electrical activity, the results from these two groups are presented together. Most electro-ureterograms were characterized qualitatively by a triphasic curve. It was not uncommon to have typical peristaltic action potentials recorded on the graph paper, but be unable to actually visualize the associated wave of peristalsis as it passed down the ureter (fig. 4). Data obtained from electro-ureterograms of dilated ureters should be presented separately from those ureters not dilated, 3 to 5 months after anastomosis of ureter to bladder or bowel.

Normal caliber ureter: The gross appearance of peristalsis was normal in force and rate. Ureterocystoneostomy or uretero-intestinal anastomosis failed to significantly alter electrical activity in the ureter. Voltages in waves 1 and 2 were normal or slightly decreased, while wave 3 was normal or slightly increased. Duration of the component curves revealed wave 1 to be normal or decreased,

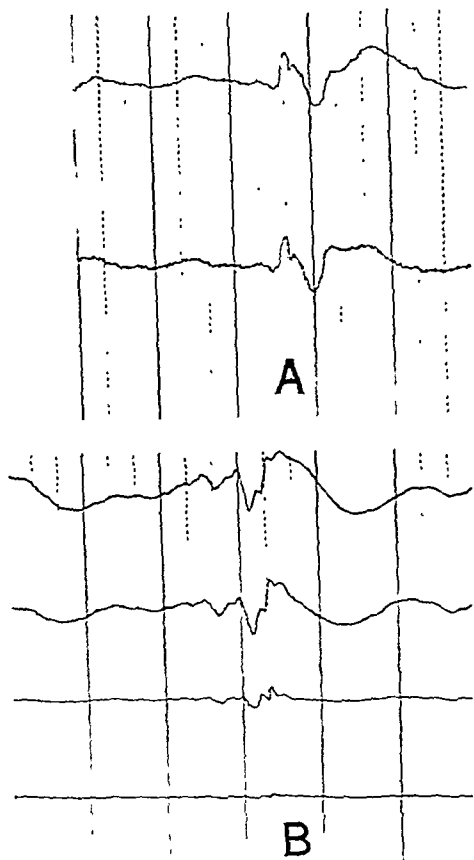


FIG 5 A, normal triphasic peristaltic action potentials in intact ureter. B, same ureter 4 months after uretero-intestinal anastomosis. No ureteral dilatation. No significant alteration in action potentials

wave 2 was normal and wave 3 was normal or slightly increased (figs. 5, 6). Although there were usually two recovery curves immediately after the electrical activity associated with peristalsis, occasionally only one curve appeared.

Dilated ureter: Grossly, peristalsis was a forceful, even violent, action. This hyperactivity was reflected in the electrical tracings. The voltage of all waves was increased. Duration of wave 1 was considerably increased; wave 2 revealed no constant change, and wave 3 was either of normal or slightly increased duration (fig. 7). Immediately subsequent to peristalsis there were usually two after-potentials that were of tremendous voltage and duration.



3) Hydration: It is well known that dehydration or increased hydration of the dog produces a decrease or increase, respectively, in renal urinary output and also affects the rate of peristalsis per unit time. Atropine, chilling of the ureter, and drying out of the ureter may also produce a change in rate of peristalsis. To demonstrate this phenomenon is extraneous to the purpose of this communication. In the present experiment it is reported that these factors failed to significantly alter the qualitative or quantitative pattern of the individual peristaltic action potentials.

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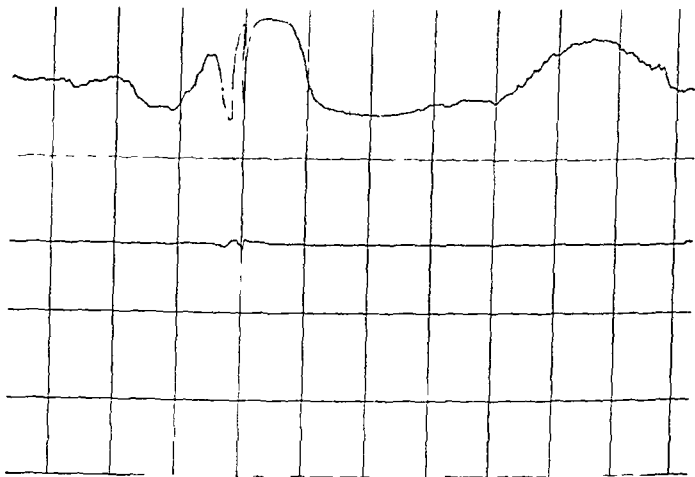


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*IV. Delayed results after incomplete occlusion of the intact ureter.* As a control experiment, four intact, but dilated, ureters were studied in 5 dogs, two to four months after incomplete ureteral occlusion by a ligature. The dilated, but intact, ureters had a normal rate of peristalsis, but the gross activity of the ureter during peristalsis was more forceful than normal. Statistically, the amplitude of wave

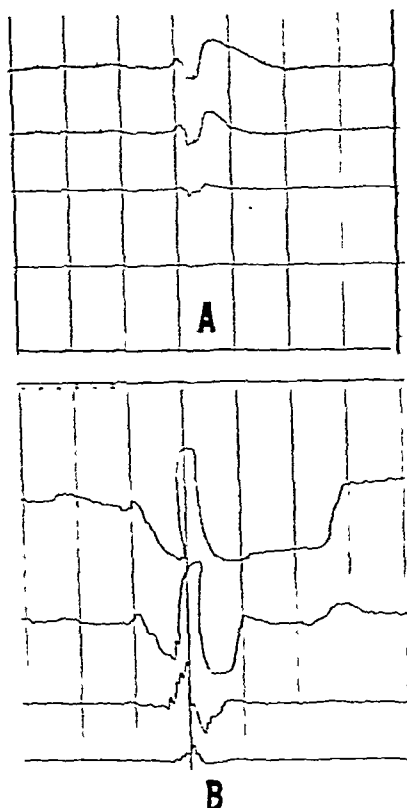


FIG. 8. *A.* normal triphasic peristaltic action potentials in intact ureter. *B.* same ureter 3 months after incomplete ligation. Ureter was dilated. Triphasic curve still present, but marked abnormalities of duration and amplitude are present. Two after-potentials demonstrated.

1 was usually slightly increased while wave 2 was increased. Wave 3 had greater voltage as compared with the normal value. Duration of wave 1 and 2 were normal, but wave 3 was markedly increased (fig. 8). Peristalsis was routinely followed by two after-potentials.

#### DISCUSSION

Living tissue is the seat of electric polarization phenomena. In the case of the ureteral muscle fibers, the polarization exists at rest and is momentarily abolished during activity. Peristalsis produces depolarization and electrical activity which are termed action potentials, and these voltages are subject to measurement. Propagated potential changes immediately precede the wave of ureteral contraction.

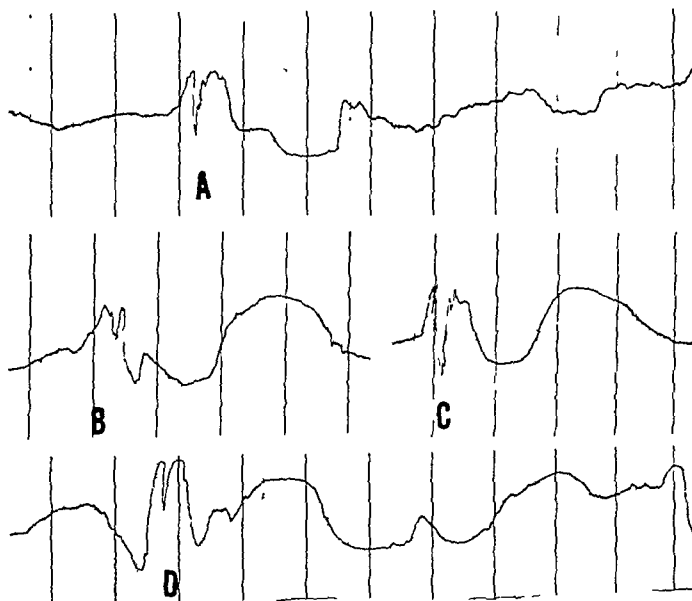


FIG. 6 *A*, normal triphasic peristaltic action potentials in intact ureter *B* and *C*, normal variants in electrical activity immediately after transection of ureter. *D*, triphasic action potentials of normal duration 4 months after uretero intestinal anastomosis. Slight increase in voltage. No ureteral dilatation.

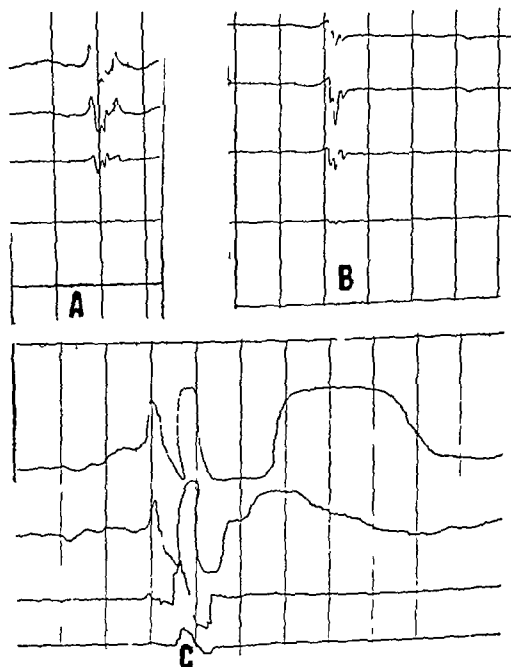


FIG. 7. *A*, normal triphasic peristaltic action potentials. *B*, no significant alteration from normal in electrical activity immediately after transection of ureter. *C*, same ureter 3 months after transection and re-anastomosis to bladder. Ureter dilated. Triphasic curve still present, but marked abnormalities of duration and amplitude are present. Two after-potentials are demonstrated.

Ureteral electromyography is a direct application of electrophysiology of the ureter to urological problems. The clinical use of this procedure is limited. It is not presumed that it should become practical and popular as electrocardiography. Considered as such, ureteral electromyography is essentially a research tool for investigating and comparing the effects of various disease states and drugs on the ureter.

### CONCLUSIONS

The normal electro-ureterogram is usually triphasic in form. An occasional normal variant may be biphasic. Transection of the ureter below the electrode and also re-anastomosis of the transected ureter to the bladder or implantation in the bowel failed to produce significant alteration of peristaltic action potentials unless ureteral dilatation developed. In control experiments these same abnormalities associated with hydro-ureter were demonstrated in the dilated but intact ureter, indicating these changes to be non-specific and related to ureteral dilatation but unrelated to impairment of propagation of conduction in a previously transected ureter.

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Although the form of the normal peristaltic action potential is apparently characterized by a triphasic curve, the amplitude of the individual waves is capable of great variation. The duration of the individual waves, however, has a considerably narrower range. During the period of recovery from peristalsis, an after-potential may occasionally be recorded in the normal ureter.

Transection of the ureter below the electrode does not produce any significant immediate alterations in electro-ureterograms. Re-anastomosis of the transected ureter to the bladder or uretero-intestinal implantation fails to produce change in duration of ureteral electrical activity, provided ureteral dilatation from anastomatic stricture does not develop. Although these ureters have normal caliber, peristaltic activity, rate, frequency and amplitude, they do have one or more after-potentials. This electrical manifestation of prolonged recovery from peristaltic contraction would indicate that these ureters are not completely normal when examined three to five months following ureteral anastomosis.

The development of anastomotic stricture and ureteral dilatation produces serious departure from normal electrical activity. In this experiment, the dilated ureter adapts to the stricture not by increase in rate of peristalsis, but by extremely forceful contractions. The total duration of peristalsis was  $183 \pm 31.2$  milliseconds in the dilated ureter, as compared with the normal mean total duration of  $108 \pm 26.7$  milliseconds in the ureter that has not become dilated after anastomosis.

To determine if the electrical abnormalities observed in the dilated ureter were due to impairment of conduction of excitation following transection and re-anastomosis to bladder or bowel, a series of intact ureters were incompletely occluded to produce ureteral dilatation. Electro-ureterograms two to four months later revealed forceful peristaltic activity of normal rate and frequency. Total duration was increased above normal to a mean of  $160 \pm 19.7$  milliseconds.

As a result of these observations it would appear that if ureteral dilatation develops in the transected ureter that has been re-anastomosed to the bladder or implanted in the bowel, there results abnormalities of peristaltic action potentials. These abnormalities are not the result of the previous ureteral transection and division of ureteral nerve supply, as nearly the same alterations are consistently observed in the dilated but intact ureter. The variations from normal are non-specific results of ureteral dilatation.

Peristaltic action potentials may usually be predicted within 10-15 microvolts amplitude and 5-20 milliseconds total duration when repeated tracings are obtained on the same ureter several months later. Occasionally, however, the graph line reveals curves which quantitatively differ considerably from dog to dog and occasionally between right and left ureters or in one ureter of the same dog. As all conditions were standardized, satisfactory explanation for these inconsistencies is lacking. All data presented are believed to be of representative electro-ureterograms from a minimum of 4 dogs in each group of experiments. The actual recording of significant electrical tracings is relatively simple when compared to the problems of interpreting these various action potential curves.

or decompensation and retention. Ultimately back pressure occurs with ureteral and pelvic dilatation as the ureterovesical musculature decompensates and permits vesico-ureteral reflux. Infection is common in these individuals with residual urine and the purely mechanical effects of stasis are complicated by the occurrence of urinary tract infection. As renal function decompensates, there is a concomitant change in the blood chemistry due to the retention of nitrogen and ultimate alterations of the acid base balance. The resultant uremia and associated urosepsis with its fatal outcome is the rule unless recognition and correction of the underlying obstructive uropathy is accomplished.

#### CASE REPORTS

*Case 1.* R. S., a boy of 11 years, was admitted to the York Hospital with the chief complaint of acute pain in the right upper quadrant, with radiation to the right loin and fever of 4 days' duration. The mother stated that throughout his entire life he had had difficulty in voiding. He had always dribbled urine with poor control. At 4 years of age pyelitis developed at which time the patient had an elevation of temperature, but since then there had been no recurrence of fever until the present episode. He had been going to school but had constant difficulties of frequency, urgency of urination and inability to properly void.

The present episode of right flank pain began 4 days prior to admission. The patient had chills with an elevation of temperature. The family physician found that the bladder was distended and advised hospital admission.

The child was acutely ill and had a temperature of 103 degrees. The head and neck were normal. The lung fields were clear. The heart was not enlarged and the tones were of good quality. The bladder was distended to the umbilicus. The external genitalia were entirely normal. The reflexes were normal.

Urinalysis: Cloudy; specific gravity, 1.012; albumin, 1 plus; sugar, negative; white blood cells, 80 to 100 per high power field; red blood cells, 6 to 8 per high power field. Urine culture: *E. coli*.

Blood Count: Hemoglobin, 69 per cent; red blood cells, 3,770,000; white blood cells, 16,000 with normal differential.

Catheterization on admission recovered 660 cc of cloudy residual urine, which when obtained was concomitant with disappearance of the suprapubic mass. The initial phenolsulfonphthalein test revealed excretion of 0 per cent in the first hour specimen and 2.5 per cent in the second hour specimen. A cystogram revealed the bladder to be well outlined with regurgitation of the solution up the left ureter and left kidney pelvis. The bladder shadow was elongated and irregular in outline. No regurgitation of dye was noted up the left ureter. The right ureter was markedly dilated and the right kidney pelvis was hydronephrotic (fig. 1, A).

Excretory urograms revealed no visualization of dye in the left kidney at any time throughout the examination. The right kidney was markedly dilated and hydronephrotic, grade 2. The patient was maintained on indwelling catheter drainage and chemotherapy. The temperature subsided and catheter drainage was continued for a period of 3 weeks, at the end of which time the phenolsul-

## CONGENITAL CONTRACTURE OF THE VESICAL NECK IN CHILDREN

H. A. GALEY AND JOHN W. BEST

*From the Urological Service, York Hospital, York, Pa.*

Congenital obstructive lesions of the lower urinary tract in infants and children are among the more uncommon conditions encountered in the average urologic practice. In no group of patients are the disastrous results of obstructive uropathy so graphically manifested as in the renal and ureteral changes and resultant chemical alterations of renal insufficiency subsequent to urinary obstruction in this younger age group. Fortunate also is the fact that in no group is the recuperative powers of the urinary tract so dramatically demonstrated as in the retrogression of morphological changes and improvement of renal function noted once the obstructive process has been relieved.

We are reporting 2 cases of congenital stenosis of the vesical neck, one in a child of 11 years and the second in a 20-month old infant. In both cases sufficient time has elapsed since the operative procedure to permit adequate follow-up evaluation.

### ETIOLOGY

The etiologic anomalies of lower urinary tract obstruction have been outlined by Eisendrath and Rolnick as 1) a very small opening in the prepuce, 2) stenosis of the external meatus of the urethra, 3) stricture of the urethra, 4) diverticulum of the urethra, 5) valve formation in the posterior urethra, 6) hypertrophy of the verumontanum, 7) contracture of the vesical neck and 8) blocking of the bladder outlet by a ureterocele or diverticulum.

There are a variety of congenital anomalies which acting separately or in combination may produce urinary stasis at or below the level of the bladder neck. Emmett and Helmholtz pointed out the difficulty in the differential diagnosis of organic obstructive uropathy and so-called neurogenic dysfunction in this younger age group. The more obvious anomalies such as pinpoint meatus and congenital stricture are, of course, self evident upon routine urologic evaluation, but the lesions affecting the posterior urethra and vesical neck offer a more difficult differential problem. Emmett and Helmholtz have divided them into 1) vesical dysfunction resulting from myelodysplasia and spina bifida and 2) congenital obstruction of the vesical neck.

These authors also point out that in their experience congenital valves of the posterior urethra as the obstructive factor are of infrequent occurrence. No instance of posterior valve formation was noted in their series of 49 cases.

### PATHOLOGICAL PHYSIOLOGY

Regardless of the etiologic cause of the obstructive uropathy the effects upon the urinary tract are those of progressive vesical muscular hypertrophy, detrusor

residual urine. His development has been normal; he is attending college and engaging in all normal activities.

Phenolsulfonphthalein tests 9 years after operation revealed a 2 hour excretion of 60 per cent.

Case 2. J. N., a 20-months old white infant boy, was admitted to the pediatric service of the York Hospital with the history of progressive abdominal enlargement for the past 4 months. At the age of 4 months the child had been operated on elsewhere for correction of a meningocele and associated spina bifida occulta. He was underweight, dribbled urine constantly and had marked difficulty in locomotion and in defecation since birth. Two other siblings were living and well.

The patient was a thin emaciated infant who appeared listless and apathetic. The abdomen was markedly protuberant, and palpation revealed a rounded tense mass which extended from the symphysis to the umbilicus. There was marked fullness noted in both flank areas. The head and neck were negative. The pupils reacted to light and accommodation. The lung fields were clear. The heart tones were of fair quality. No murmurs were elicited. The external genitalia were essentially negative. The rectal sphincter exhibited good tone. No rectal masses were palpable.

Urinalysis: Cloudy; alkaline in reaction; specific gravity, 1.005; albumin, 2 plus. Microscopic: Specimen was loaded with white blood cells. Urine culture: B. coli in heavy growth.

Blood count: Hemoglobin 57 per cent; red blood cells, 3,500,000; white blood cells, 7,000 with normal differential. Blood urea nitrogen: Initial, 40.5 mg. per cent.

Catheterization recovered 500 cc of cloudy residual urine. A cystogram made with the child in the Trendelenburg position revealed a large hypotonic bladder with a reflex of the dye upward into the markedly dilated ureters and extensive bilateral hydronephrosis (fig. 2, A).

A barium enema revealed moderate dilatation of the colon throughout with only slight evidence of normal haustral markings.

An initial diagnosis of neuromuscular dysfunction of the urinary tract with a hypotonic bladder and megalo-ureter and bilateral hydronephrosis was made.

The situation was discussed with the family and the referring physician, and the child was referred to another clinic for further evaluation. It was the impression of the consulting group that this represented a progressive neuromuscular dysfunction of the urinary tract related to the meningocele and spina bifida occulta noted at birth. The opinion was given that the prognosis was hopeless and no treatment was advised. Following return from the clinic the pediatrician and family consulted us regarding future progress of the child.

The child was re-admitted to the hospital and an exploratory operation was advised in the hope that the urinary tract dysfunction might be on an obstructive rather than a purely neurogenic basis.

Following a 2 week period of indwelling catheter drainage and antibiotic therapy to combat the secondary urinary tract infection, a suprapubic exploration was carried out. The bladder was markedly thickened and trabeculated.



fonphthalein had improved to a 23 per cent excretion of dye in the first hour and 12 per cent in the second hour, a total of 35 per cent excretion. The diagnosis of obstructive uropathy primarily in the vesical neck, with secondary infection and dilatation of the upper urinary tract was established.

Operation: A suprapubic incision was made and the bladder was exposed. The bladder wall was markedly thickened, measuring 1 cm. in thickness. There was marked bladder trabeculation and exploration revealed the vesical orifice to be markedly contracted so that it was impossible to introduce the tip of the index finger. The contracted vesical orifice was resected by sharp and blunt dissection and the posterior urethra was progressively dilated so that the index

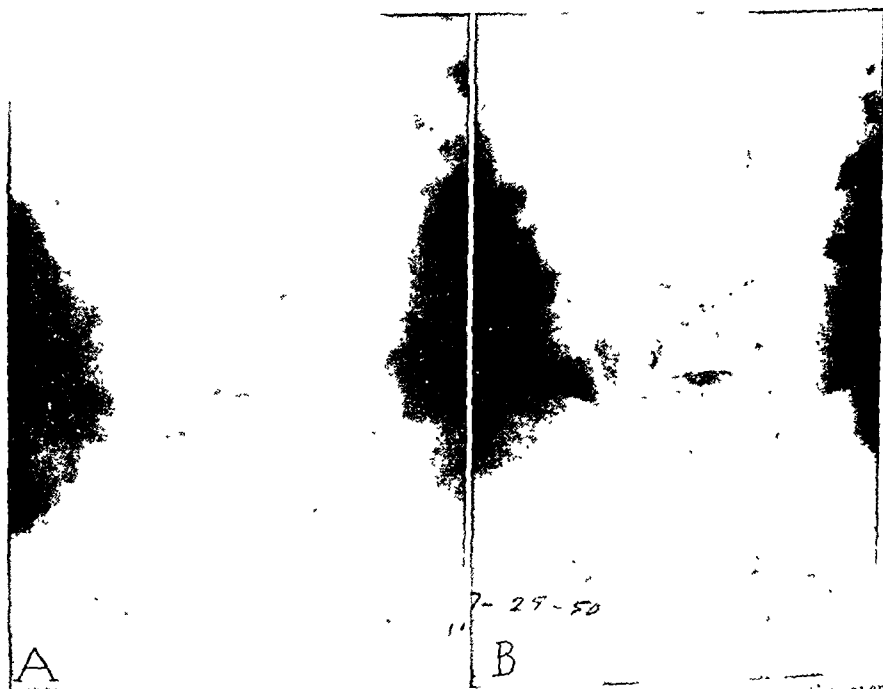


FIG. 1. Case 1. *A*, preoperative cystogram with ureteral reflux. *B*, postoperative excretory urogram.

finger could easily be introduced through the vesical orifice. The bladder was then closed about a cystotomy tube.

The postoperative course was uneventful, and the suprapubic tube was removed on the ninth postoperative day. The patient voided satisfactorily in amounts varying from 2 to 6 ounces. He stated that the stream was forceful and much fuller than before his operative procedure.

Two days prior to discharge from the hospital excretory urography revealed satisfactory visualization of the right kidney and ureter with some diminution of the hydronephrosis. The left kidney was not visualized.

Postoperative progress evaluations have been made at intervals for 9 years. Progress pyelograms (fig. 1, *B*) reveal moderate reduction in the hydronephrosis and hydro-ureter on the right. The patient is voiding a good stream with no

residual urine. His development has been normal; he is attending college and engaging in all normal activities.

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Exploration revealed a marked contracture of the vesical neck and posterior urethra. The vesical neck contracture was resected by sharp dissection and the posterior urethra widely dilated. A suprapubic cystotomy tube was inserted and the vesical wound was closed.

The child's postoperative convalescence was uneventful. The suprapubic tube was removed on the tenth postoperative day. The wound healed uneventfully and the child voided an excellent stream with fair control. The child was discharged from the hospital on the nineteenth postoperative day at which time the suprapubic wound was practically healed and the child was voiding per urethram. Determination of the residual urine the day prior to hospital discharge revealed  $\frac{1}{2}$  ounce of slightly turbid urine.

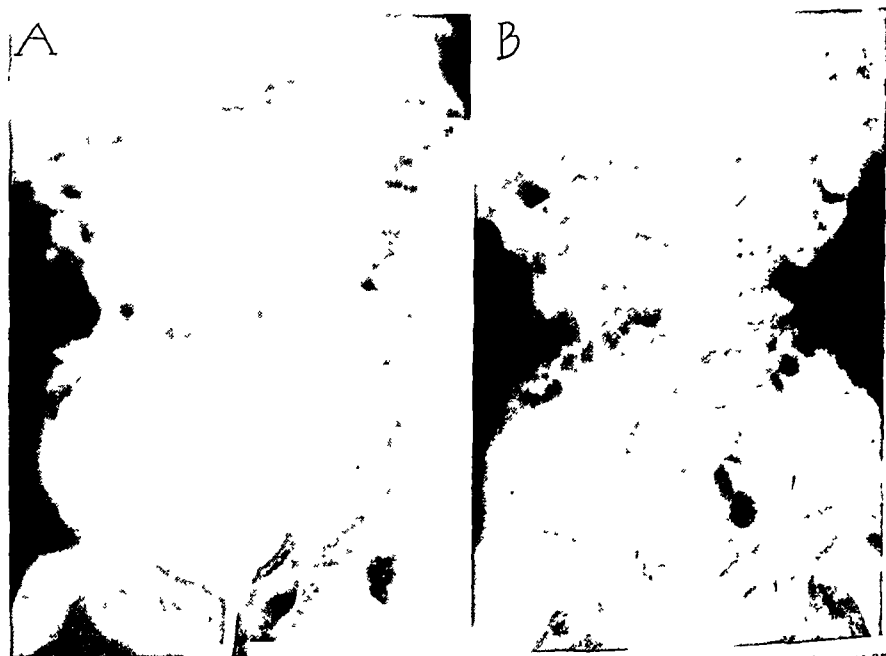


FIG. 2 Case 2 A, preoperative cystogram with ureteral reflux. B, postoperative excretory urogram.

The child's subsequent progress has been most satisfactory. He has gained in weight, his appetite has improved, and the mother stated he voids an excellent stream although there is at times some terminal dribbling. Progressive urethral dilatations have been carried out at intervals of 3 months and the channel has been maintained at 16F.

Excretory urograms 3 months postoperative revealed the kidneys to be normal in size, shape and position. The right kidney showed only a mild degree of calyectasis and on the left the calyces had returned to apparently a normal configuration. The ureters were normal in appearance (fig. 2, B). The postoperative results and retrogressive changes of this urinary tract following surgery were most gratifying.

The child was seen 2 years postoperative and the residual urine determination revealed no evidence of residual urine. The child was voiding a good size stream

with occasional terminal dribbling. He has gained in weight and strength, and the pediatrician reports that the child's progress is normal for one in his age group.

#### DISCUSSION

The obstructing lesion in both of these cases consisted of a marked contracture of the vesical neck with resultant obstructive uropathy and secondary infection. As previously pointed out, Emmett and Helmholtz have suggested in their series that the existence of congenital valves as the obstructing lesion would appear much less common than generally supposed. Our brief experience in these 2 cases would tend to support that view.

In case 1, the child of 11 years, the process had been of long standing and complete destruction of the left kidney as a functioning unit had occurred and the changes on the opposite side were advanced at the time of diagnosis.

The necessity of complete urologic investigation of all cases of chronic or recurrent pyuria or urinary difficulty in children is emphasized in order that earlier diagnosis and subsequent correction of such congenital obstructive uropathic lesions may be carried out.

Most recent reports appear to favor the transurethral approach in the correction of these vesical neck contractures in infants and children. Our familiarity with open surgical exposure led us to utilize the suprapubic route in our cases. The approach would appear to be one of personal preference.

In case 2 the child had associated neurologic anomalies consisting of spina bifida occulta and meningocele, and it was first supposed that the urinary tract findings were on a congenital neurogenic basis. However, in spite of this assumption at exploration the pathological process was an obstructive lesion of the vesical neck. Postoperative retrogression of the renal and ureteral dilatation evidenced by progress pyelograms would lead us to believe that all such cases are entitled to operative exploration as a measure which may well be life-saving in this group of patients.

#### CONCLUSION

Two cases of congenital contracture of the vesical neck in children with satisfactory operative results are presented. The necessity of urologic investigation in all cases of chronic or recurrent pyuria or urinary tract difficulty in children is emphasized so that earlier diagnosis and subsequent correction of the obstructive uropathy may be accomplished before irreparable renal damage has occurred. In view of our experience, we would urge in those cases in which associated congenital neurologic anomalies are present and the diagnosis of neurogenic dysfunction of the bladder seems established, that congenital contracture of the vesical neck be considered and operative exploration if necessary be utilized to correct the obstructive lesion if present. The results may be most gratifying.

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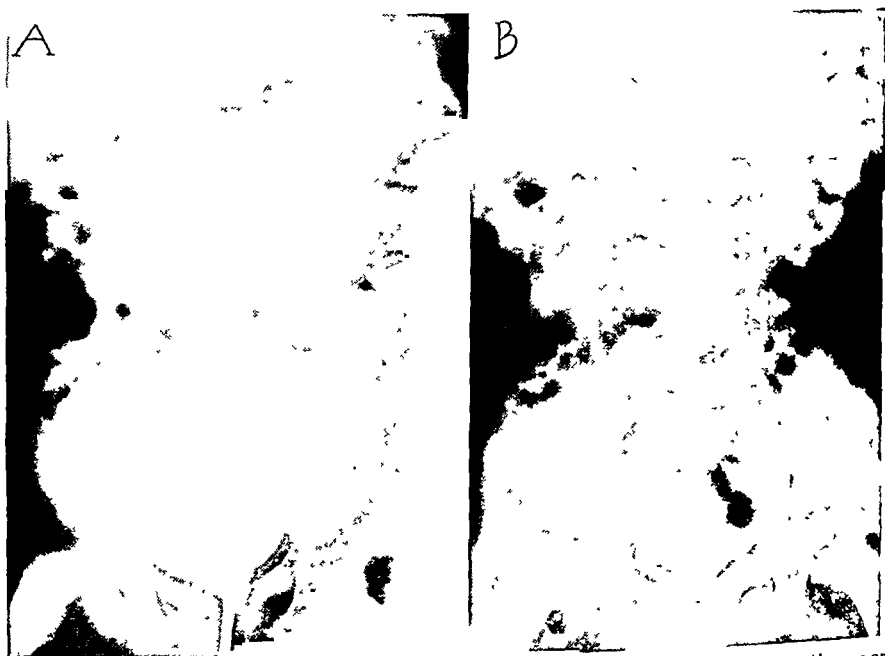


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## INTERSTITIAL CYSTITIS IN CHILDREN

HAROLD P. McDONALD, WILBORN E. UPCHURCH AND  
CLINTON E. STURDEVANT

*From the Urological Department of St. Joseph's Infirmary, Atlanta, Ga.*

"Interstitial cystitis," "Hunner's ulcer," "localized submucous fibrosis," "elusive ulcer of the bladder" are all synonymous terms used to name an entity which has been found to be extremely difficult to treat satisfactorily. A search of the literature fails to reveal reports of its occurrence in young children. However in a series of 63 patients Barnes mentioned a child of 7 years and Hand reported one 13 year old girl in a series of 213 patients. Higgins' youngest in 100 patients was 17 years. Interstitial cystitis, mentioned as early as 1836 by Mercier, was described completely both from standpoint of pathology and classical clinical picture in 1914 by Guy Hunner of Baltimore. Since this report very little new has been added as to etiology or pathology, although many excellent articles have appeared in the literature. It has been shown to occur more frequently in females over males in ratio of about 10 to 1.

Recommended treatment has varied from bladder dilatations, with fulguration of affected areas, injections of silver nitrate of increasing strengths, subtotal cystectomy, diversion of the urine by ureterocutaneous or ureterosigmoid route, injection of novacain or alcohol into the submucous layer of the bladder and the administration of various drugs. Recently the use of cortisone and bantnine has been reported favorably. Many other measures and drugs have been tried but with notable lack of uniform success.

This report does not offer a new method of therapy, nor does it offer anything new as regards the etiology of interstitial cystitis. However, by establishing the fact that children not infrequently have this type of cystitis a new field of investigation as to etiology may be stimulated. Also many children formerly classified as psychotic or psychological enuretics may be exonerated. I should like to say that the term psychological enuresis has never appealed to, nor satisfied us; we have believed that a child would not continue to wet the bed if it is within his power to stop. In pursuing this premise we first recognized interstitial cystitis in a  $4\frac{1}{2}$  year-old girl  $2\frac{1}{2}$  years ago. Since that time we have seen five additional patients, all girls, varying in age from 3 to 10 years, and all of whom had typical areas of interstitial cystitis. All patients have had complete urinary tract examinations, excretory urograms, cultures, retrograde pyelo-ureterograms and bladder capacity measurements. Upon over-distention of the bladder under anesthesia all have exhibited typical areas of interstitial cystitis, unmistakable, red, blotchy, irregular hemorrhagic spots. The clinical course of all these patients has been similar, varying only in degree of response to treatment. These patients have been graded 1, 2 and 3 according to the degree of involvement as evidenced by response to therapy. Treatment mainly has consisted of dilatation of the bladder under anesthesia and fulguration of the affected hemorrhagic area. Dilatations of the bladder by means of irrigations followed by instillation of silver

nitrate in gradually increasing strength has constituted the follow-up treatments. Additional bladder dilatations under anesthesia and fulguration of the areas of interstitial cystitis have been done based on the response to the above. Two patients have been graded 3; three have been graded 2, and one has been graded 1.

#### CASE REPORTS

*Case 1.* N. G., a girl  $4\frac{1}{2}$  years old, first seen March 1950, had had enuresis, frequency and wet pants during day all her life. Excretory urograms were normal; urine culture sterile. The bladder capacity under anesthesia was found to be 4 ounces. No improvement in symptoms followed urethral meatotomy and urethral dilatations. Attempts at bladder dilatation were unsuccessful; fluid ran out around catheter after injection of 4 ounces. Cystoscopy was repeated and dilatation of bladder up to 5 ounces under anesthesia showed blood-tinged fluid. Inspection of bladder revealed the presence of areas typical of interstitial cystitis in the posterior and left lateral walls. Fulguration of these areas and repeated bladder dilatations and irrigations of silver nitrate solution resulted in a maximum bladder capacity, under anesthesia, of 6 ounces. Banthine had been administered for periods of 30 days with little or no effect. The patient, now 7 years old, continues to have enuresis but has largely ceased wetting her pants during the day. At the present time further dilatations under anesthesia and fulguration to the affected areas appear to be the best plan to afford improved bladder function. This case was classified grade 3.

*Case 2.* B. J. B., a girl aged 3 years, when first seen in August 1951 had had enuresis, wet pants during day and recurrent pyuria with fever all her life. Competent urologists elsewhere found the upper urinary tracts normal. Antibiotic therapy cleared urine in each instance of pyuria but had no effect on the enuresis and wet pants during the day. Excretory urograms were repeated; the findings were normal with the exception of slight dilatation of the lower ureters. Cystoscopy revealed bladder capacity of 5 ounces. Interstitial cystitis was not found but inflammatory masses seen at the vesical neck were resected. No improvement was noted in regard to the enuresis or wet pants. Three months later cystoscopy was repeated and the bladder capacity, under anesthesia, again was found to be 5 ounces. Upon forcible injection of additional fluid, hemorrhagic areas typical of interstitial cystitis were seen to appear in posterior bladder wall. These were fulgurated. One month later much improvement was noted in the symptoms; no enuresis and no wet pants. Thirty days later continued improvement, bladder dilated to 7 ounces. Two months later the bladder was dilated to 8 ounces and areas of interstitial cystitis were again fulgurated. This child, now  $4\frac{1}{2}$  years old, proudly exhibited her dry pants when she came in for examination and treatment about one month ago.

*Case 3.* M. H., a girl aged 4, when first seen October 1951 had had enuresis, urgency, wet pants, and slow voiding all her life. Excretory urograms were normal as were retrograde ureteropyelograms. Examination of the vesical mucosa showed trabeculation, and the vesical neck was found to be hypertrophic. Transurethral resection was done and obstructing tissue removed with the 16F resecto-



scope. Improvement in voiding followed this procedure but enuresis and wet pants during the day continued. Cystoscopy again done and bladder capacity under anesthesia was found to be 6 ounces. Upon dilatation to 8 ounces two hemorrhagic areas typical of interstitial cystitis were seen back of the trigone and on the right lateral wall of the bladder. Fulguration of these areas and subsequent bladder dilatations have resulted in improvement in symptoms but enuresis continues. The case was classified grade 2.

*Case 4.* D. S., a girl aged 10 years when seen July 1950, had had enuresis all her life, and wet pants until recently. Now urgency was present to point of incontinence, if it were impossible for her to void promptly upon urge. Excretory urograms were normal. Cystoscopy revealed normal upper urinary tracts. Urine culture was sterile. Bladder capacity under anesthesia was 3 ounces. Dilatation of the bladder showed typical areas of interstitial cystitis in the posterior wall. Fulguration of these areas was done followed by bladder dilatations at intervals of 3 to 6 weeks until March 1952. A bladder capacity of 12 ounces without anesthesia was attained, the symptoms were entirely relieved but additional bladder dilatations have been recommended. The case was classified grade 2.

*Case 5.* S. C., a girl aged 6 when first seen in January 1952, had had enuresis all her life, and urgency with wet pants occasionally. Excretory urograms were negative except for slight dilatation of the lower portion of right ureter. Upon cystoscopy inflammatory masses in vesical neck were found and bladder capacity of 6 ounces. One area typical of interstitial cystitis was observed in lateral wall of bladder above left ureter. Fulguration was done of inflammatory masses in vesical neck and also area of interstitial cystitis. The symptoms improved immediately and subsequent dilatations of bladder at 3 to 4 week intervals have now resulted in a capacity of 10 ounces. The symptoms have been entirely relieved but treatment advised to be continued. The case was classified grade 1.

*Case 6.* C. Z., a girl aged 8 when first seen February 1952, had had enuresis all her life and also wet pants during day. Excretory urograms were normal. Cystoscopy revealed maximum bladder capacity under anesthesia of 6 ounces. The vesical neck showed inflammatory masses which were resected with a 16F resectoscope. Slight improvement was noted in symptoms but enuresis continued and also occasional wet pants in day. Cystoscopy repeated and the bladder dilated to 8 ounces whereupon an area typical of interstitial cystitis was seen in posterior bladder wall. Fulguration of this area was done and subsequent bladder dilatations at 3 to 6 week intervals. The bladder capacity is now 10 ounces and the child does not wet her pants day or night. The case was classified grade 2.

#### COMMENT

These 6 patients, all girls and all with typical findings of interstitial cystitis, have caused us to re-evaluate all children seen by us for bladder complaints during recent years. It is our belief that many children suffering from enuresis, urgency or wet pants during the day, who fail to respond favorably to meatotomy, urethral dilatation and vesical neck fulguration may have reduced vesical capacity because of interstitial cystitis. Since all these children with interstitial cystitis

have been girls (and since the ratio of women to men with interstitial cystitis is about 10 to 1) the theory of recurrent low grade infection as etiology seems reasonable. This theory is not new but seems to be strengthened in the light of foregoing points. Additional investigation may bear out the worth of these thoughts. It should be emphasized that this is really but a preliminary report and must be verified by others. At the present time interstitial cystitis unsuspected and undiagnosed appears to answer former failures to cure enuresis and urgency in some patients seen before this condition was suspected and recognized.

#### SUMMARY

Interstitial cystitis has been found to occur not infrequently in children. Six cases, all girls varying in age from 3 to 10 years, have been reported.

*57 Forsyth St. N.W., Atlanta 3, Ga.*

## ADULT MALE ENURESIS: A STUDY OF 200 CASES

ROBERT B. ZUFALL, CAPT. (M.C.)

This study was made in the hope of helping to clarify a common problem about which there is a remarkable divergence of opinion as to etiology, pathology, treatment, and even frequency of occurrence. The most important questions about this condition seem to be, first, "What is the relationship of bed wetting to what organic diseases?" and, second, "What treatment will cure it?" This is a report of 200 enuretic soldiers between the ages of 17 and 25, personally seen and treated during the past year at Fort Leonard Wood, Missouri. Conclusions presented are in some respects controversial but none the less they seem definitely valid for this group of cases.

Enuresis in children has been excellently described by Meredith Campbell<sup>1</sup> who has seen over 1500 cases. He stresses the fact that, although 90 per cent are purely "functional," enuresis may be the presenting symptom of serious organic disease. He is convinced that the etiology in most cases is emotional insecurity, distress, and the desire for attention in a child of parents who may be either inattentive or more often highly emotional, neurotic, insecure people themselves. The organic diseases he has found in so-called enuretics include congenital obstructions, neurological disease, ectopic ureters, urethral diverticula, and the perhaps less well defined entities of weak sphincter, prostatitis, verumontanitis and polyps of the verumontanum. He states that uropathy is found in 60 per cent of cases resistant to medical and psychiatric therapy. H. P. Winsbury-White<sup>2</sup> found organic disease in 70 per cent, mostly mild posterior urethral inflammation which he treats with sounds and silver nitrate solutions. D. L. Cohen<sup>3</sup> found organic disease consisting of shortening of the trigone, depression between the verumontanum and bladder neck, and other minor changes in twenty-four out of 25 enuretic soldiers.

Campbell states that there is no good drug for the treatment of functional enuresis. Benzedrine,<sup>4</sup> ephedrine,<sup>5</sup> testosterone,<sup>6</sup> belladonna and sedatives all have their advocates. He has had little success with alarms and mechanical devices, and recommends psychotherapy. Others have suggested presacral neurectomy,<sup>7</sup> construction of a urethral sling,<sup>8</sup> and lumbopubic electric shock. Brief psychotherapy was used by Kriegman and Wright<sup>9</sup> in 25 soldiers, with cure in sixteen and improvement in four. This consisted of explaining to the patient the functional nature of his complaint, telling him that he could improve, accepting

Accepted for publication November 4, 1952.

<sup>1</sup> Campbell, Meredith: *Clinical Pediatric Urology*. Philadelphia: W. B. Saunders Co., 1951.

<sup>2</sup> Winsbury-White, H. P.: *Brit. J. Urol.*, **16**: 81-102, 1944.

<sup>3</sup> Cohen, D. L.: *J. Urol.*, **57**: 331-337, 1947.

<sup>4</sup> Strom-Olsen, R.: *Lancet*, **2**: 133-135, 1950.

<sup>5</sup> Rudolph, G. DeM.: *J. Ment. Sc.*, **94**: 629-640, 1948.

<sup>6</sup> Kugelmass, I. N.: *N. Y. State J. Med.*, **47**: 1369-1370, 1947.

<sup>7</sup> Brodny, M. L. and Robins, S. A.: *J.A.M.A.*, **126**: 1000-1006, 1944.

<sup>8</sup> Bonino, M.: *Urologia*, **15**: 87-95, 1948.

<sup>9</sup> Kriegman, G. and Wright, H. B.: *Am. J. Psychiat.*, **104**: 254-258, 1947.

him as a person, though not accepting his enuresis. In later interviews there was increasing strictness and scolding on the part of the psychiatrist

#### ETIOLOGY AND PATHOGENESIS

We found enuresis a common condition in young adult males. The figure of 25 per cent of men of draft age has been quoted<sup>7</sup> and seems reasonable. During the time that 100 cases of enuresis were seen at this hospital, 187 hernia repairs were done. The fact that most urologists see almost no cases must be explained on the basis that most of these men have either never seen a doctor or have seen their family doctors when they were children and been discouraged from further attempts to find a cure. Only eight of the 200 cases in this series had ever seen a urologist or had a complete urologic workup. No organic disease was found in the vast majority of our cases, and in none was serious organic disease discovered. All patients had a detailed history, local physical examination and routine and microscopic urinalysis. Coronal adhesions were found once, meatal strictures twice. The latter were opened, but enuresis did not improve. Neurological abnormalities and evidence of hormonal imbalance were not found. Urinalyses showed a normal range of specific gravities, most of them around 1.020, only 20 below 1.015. In these cases the urine was otherwise normal except for 2 patients who had red and white cells on microscopic examination. They had cystoscopic evidence of acute hemorrhagic cystitis. Retrograde pyelograms with urine cultures were normal, and the cystitis in both cases improved without improvement in the enuresis.

Further workup was done on several other cases. Nine plain urograms, 16 excretory urograms, 4 retrograde pyelograms, and 10 cystometrograms were normal. In 60 cases panendoscopy was performed with the No. 24 McCarthy instrument, without anesthesia. Sensation was normal in all. Mild trabeculation was found in three, large verumontanum in four, red and granular verumontanum in three, slightly elevated bladder neck in four. The remainder appeared perfectly normal. No residual urine was present in 28 cases, 10 cc in 10 cases, 30 cc in 3 cases, and in none was it higher. Prostatic smears on 13 patients averaged  $5\frac{1}{2}$  white blood cells per high power field. In only 2 cases were there over 8 white blood cells. These patients did not respond to prostatic massage. It would seem significant that patients with severe cystitis, prostatism, et cetera, do not complain of enuresis even though they may be getting up 10 times a night to void.

The psychogenic element was quite apparent. These cases fell into a definite personality pattern, strikingly the same as that reported by Kriegman<sup>9</sup> and Shhonsky<sup>10</sup> in similar groups. After brief interview, personalities in 95 patients were classified as quiet, shy, and awkward in thirty-two, slow and rather stupid in fifteen, dependent with many neurotic complaints in ten, five were anxious, three, homesick, three, aggressive, five prisoners from the stockade. Seventeen seemed normal, pleasant, and straightforward, while five appeared more than usually intelligent and educated. The characteristic personality type seemed to be the emotionally immature, passive, dependent individual, who had not had "sufficient warm acceptance, firm support, and permissiveness in his relation-

<sup>10</sup> Shhonsky, H. *War Med*, 7: 297-303, 1945.

ship to significant adults."<sup>9</sup> It has been suggested that the enuresis represents both an expression of resentment and of the desire to be considered and protected like a child.

They were of average or low average intelligence, were mostly white (of 112 cases, seventy-seven were white and thirty-five Negroes). Most had had some schooling. Of 70 cases, seventeen had finished 8 grades, forty have gone to high school, eleven completed high school, two gone to and one completed college. Out of 83, there were 51 unskilled laborers, 16 farmers, 9 truck drivers. There were also 1 schoolteacher and one who had owned his own business. Of 92, seventy-six were single, sixteen married. Of 136, one hundred and twenty-eight were privates, four privates first class, three corporals, one a sergeant. No higher ranks were represented.

In 129 cases, brief questioning elicited some sort of serious family trouble. Thirty-five were poor, thirty were orphans, twenty-six had one or both parents chronically ill, sixteen had families who were separated, seven had families who were divorced, and a scattering with anxious or nervous parents, family fights, father a drunkard or in jail. One patient was illegitimate. In only eight was the family life described as all right on even brief questioning. Most patients had 3 or 4 siblings. Family history of enuresis was high, there being 125 enuretic relatives in the group, mostly brothers (56). The question of some inherited abnormality has been raised, but not solved.

The incidence of associated neurotic complaints was high. Eighty-eight out of 100 patients had day frequency and precipitancy of urine, and a few had wet their pants. Sixty-seven out of 103 had back pains, nineteen had leg or abdominal pains, eight had headaches, ten nervousness, five dysuria, one each asthma, urinary retention, urethral discharge, and fainting spells. For none of these was any organic basis found.

Enuresis had been lifelong in 133 out of 149 cases. Two dated onset from an injury to the perineum or back, though no evidence of injury could be found. In 9 cases, enuresis developed while in the Army, one of these following the death of both parents, two after Korean service, one after hernioplasty. One followed scarlet fever in adolescence. Out of 113 patients, wetting occurred nightly or almost nightly in forty-one, at least once a week in fifty-six, and less often in sixteen. Rarely was there any change through the years. One might note that it seems hard to imagine an organic disease cropping up at weekly intervals for 25 years, leaving no physical sign of its presence.

Malingering was rare if not absent. Twenty-five of these men had volunteered for the Army and wanted to stay in. The history in most of the others was so typical that it is hard to believe it was invented. Many had letters from their family doctors certifying to their enuresis prior to entry into service.

A certain indifference to treatment was noted in many cases. Twelve refused cystoscopy, several complained bitterly that the benzedrine given for their enuresis kept them awake. Nineteen had had no treatment prior to entry into service. This may reflect the attitude of family or of family doctor, or the patient's discouragement with previous treatment; but it seemed to be more the *belle indifference* of the neurotic, suggesting a subconscious desire to keep his symptom because it serves a purpose.

Diabetes and seasonal variation were not found. Thirty-seven patients considered their sleep light or normal as against twenty who believed that their sleep was abnormally deep. Thirty-nine were city dwellers versus 36 from the country.

#### TREATMENT

Medical and urologic treatment in this group was unsatisfactory. All the commonly recommended treatments were tried. Although good results have been reported, we found none of much value. Thirty-four out of 79 patients had previously been treated by their family doctors, eighteen had used patent medicines, and eight had had apparently complete urologic workup, all without any success.

Banthine 100 mg. 4 times a day by mouth was given for 2 to 4 week periods to 10 patients, all of whom had negative cystoscopy, pyelograms, and cystometric studies. Bed checks were done in the hospital. There was no change in the frequency of wetting. Benzedrine 20 mg. by mouth at bedtime for 1 or 2 weeks was used in 53 cases, on the theory that it would help if enuresis was due to abnormal depth of slumber. Forty-three were unimproved, nine a little improved, one markedly improved. None were cured. Tincture of belladonna, 15 drops 4 times a day by mouth for 1 or 2 weeks was used in 39 cases. Thirty-three were unchanged, 6 improved, none cured. Methyl testosterone linguets, 5 mg. 4 times a day were used for 1 week periods in 3 cases, without improvement. Sedatives, such as phenobarbital, nembutal, and amytal, were used in 5 cases, without benefit. Cysto-urethroscopy with the 24F instrument, which would seem comparable to adequate sounding, resulted in no change in the 60 patients on whom it was done. Cauterization of the posterior urethra with 4 per cent silver nitrate was done in 6 cases, without change in symptoms. Surgical construction of a urethral sling, neurectomy, and lumbopubic electric shock were not tried. It was believed that they might do more harm than good. Psychotherapy was not used per se in our series, though it may well account for the occasional improvement noted.

Disposition in most cases has been discharge from the Army on the recommendation of the psychiatrist because of immature personality with symptomatic habit reaction. A few patients have been retained in service. Prognosis for cure would seem to be bad. Followup studies on these patients after they return to civilian life are planned.

#### SUMMARY

Two hundred cases of enuresis in soldiers have been reviewed. Though it should definitely be emphasized that enuresis, especially in children, may be the tip-off to serious organic disease, it is believed that the symptom in adults is almost always a psychogenic one. The role of vaguely defined irritative conditions of the posterior urethra in causing enuresis has probably been overestimated. Certainly careful history, physical examination, and urinalysis should be done in every case. Further workup should be determined from that point. If the history is typical and the physical and urine negative, there would seem to be little need to do cystoscopy or further urologic studies. Treatment in this series, including banthine, has been unsatisfactory. Psychotherapy may be the answer.

*32 Lenox Road, Rockville Center, N. Y.*

## ADENOFIBROMA OF URINARY BLADDER: A CASE REPORT

MAX LEVI AND CYRIL SOLOMON

This case is presented because no similar case can be found in the literature. R. G., a 46 year old white man, was first seen on November 30, 1949 for burning on urination since 1947. He had one episode of hematuria at which time an excretory urogram was said to be negative. He had a herniotomy done in May 1949. The burning on urination continued.

An excretory pyelogram revealed a large filling defect in the left side of the bladder, normal kidneys and ureters. Cystoscopy showed a tumor about 3 by 2 cm. in size on the left posterior bladder wall obstructing the left ureteral orifice and having a smooth surface covered by normal mucous membrane. The anterior part was divided in two heads; in the saddle between them were numerous tiny elevations. Indigo carmine appeared in 3 minutes from the right ureteral orifice; none was visible on the left side.

The biopsy was inconclusive because of the extreme hardness of the tumor. However, the cystoscopic appearance was benign and conservative surgery was decided upon.

Suprapubic cystotomy was performed at Terrace Heights Hospital on December 12, 1949. When the tumor was elevated the left ureteral orifice became visible and urine was seen spurting from it. The tumor was resected in two pieces with a Lichtenberg-Heywalt snare. There was no evidence of infiltration. The patient was discharged on December 22. Postoperative and follow-up cystoscopies were normal.

The gross specimen consisted of multiple fragments of tissue, measuring in the aggregate 5 cm. All were necrotic and showed on the surface a cauliflower-like growth. In some areas cyst formation of the surface epithelium was present but there is no evidence of ulceration. The stalks of these papillary projections were firm, fibrous and edematous.

Multiple sections of the tumor revealed it to consist of duct-like structures which were contained within fibromuscular tissue. Close to many of the ducts the fibromuscular tissue was myxomatous in character. Papillation was present within the ducts which in some areas were lined by unilayered cuboidal epithelium and other areas appeared to be lined by transitional cells, while islands of epithelium were present within which there were spaces containing a pink-staining amorphous material. A moderate lymphocytic reaction was present throughout the entire tumor. Congestion was moderate in amount. Near the surface of the tumor were crypt-like spaces into which the transitional epithelium dipped. Mitotic figures were sparse and the cells were not atypical. In one area the epithelium was mucosecreting in character. Ulceration of the mucosa was noted with some necrosis and a dense lymphocytic reaction.

Diagnosis: Adenofibroma of the urinary bladder (fig. 1).

Because of the pathological interest in the case, the tumor was sent to the

Accepted for publication November 25, 1952.

Registry of Urology at the Armed Forces Institute of Pathology. The Registry believed it to be a mesonephric remnant in the bladder wall and submitted the material, because of the unusual interest, to several consultants. Two of them were of the opinion that the tumor was a fibro-adenoma and one believed it to be an inclusion tumor of primordial nephrogenic origin.

In a review of the literature only one article<sup>1</sup> has any similarity to the case reported. The pathogenesis of this tumor is of interest and there is a question as to its origin from mesodermal anlage or whether it is a true neoplasm. It would

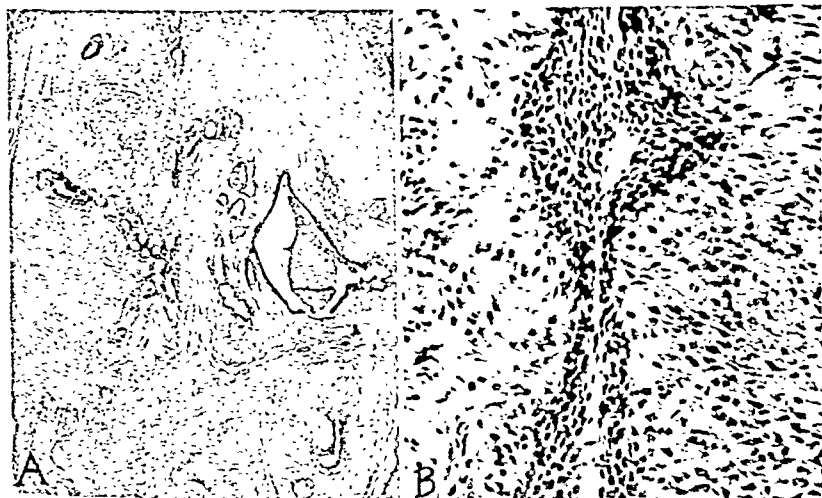


FIG. 1. A, low power view of nodule revealing glandular element with surrounding fibrous tissue. B, epithelial clefts with surrounding myxomatous fibrous tissue.

be difficult to explain on a basis of mesonephric rests, and we believe it to be a true neoplasm.

It should be emphasized that the possibility of a benign lesion of the bladder, while rare, does occur and treatment should be conservative.

In summary, 1) a case of adenofibroma of the bladder is reported; 2) benign tumors of the bladder, while rare, should be treated conservatively.

We want to thank Dr. L. Marienberg who referred the case and the members of the Registry for their interest and cooperation and for the excellent photomicrographs.

200 Central Park South, New York 19, N. Y.

<sup>1</sup> Paschkis, R.: *Ztschr. f. urol. Chir.* 21: 315-325, 1927.



## SARCOMA BOTRYOIDES OF THE BLADDER IN CHILDREN

WILLIAM H. MORSE (CAPT. MC) AND W. DABNEY JARMAN

*From the Urology Section, Surgical Service, Walter Reed Army Hospital, Washington, D. C.  
and Children's Hospital, Washington, D. C.*

Approximately twenty cases of polypoid sarcoma of the bladder in children have now been reported. Their cystoscopic appearance and clinical course have been so similar that they should be considered as a single clinical entity, in spite of the variable pathological diagnoses such as rhabdomyosarcoma, myxosarcoma, myomyxosarcoma, myxoma, and benign multiple polyps.

In the past, a lack of familiarity with this particular lesion has led to prolonged hopeful temporizing in the treatment of this highly fatal disease. It is imperative that close co-operation exist between the urologist and the pathologist in evaluating the character of this lesion.

In May 1952, Mostofi and Morse<sup>1</sup> reviewed the cases of sarcoma botryoides, or polypoid rhabdomyosarcoma, in the Bladder Tumor Registry. Ten cases were analyzed and these constituted the largest group of cases in which the clinical findings, results, and gross and microscopic findings could be reviewed. The tumor was found to be almost uniformly fatal within 24 months.

An attempt to tabulate the number of case reports has been difficult and misleading because of the difference in naming what appears to be a single clinical entity.

The term "polypoid rhabdomyosarcoma" has been suggested for this group of polypoid, grapelike, translucent bladder tumors in children, but all of the tumors do not have the giant cells or the striated "strap" muscle cells. All, however, have the distinct myxomatous, grapelike, gross appearance which would seem to justify the term "sarcoma botryoides," coined by Pfannenstiel.<sup>2</sup>

The importance and difficulty of establishing an early diagnosis can be illustrated best by the presentation of 2 case reports of infants with sarcoma botryoides.

Case 1 demonstrates how misleading multiple biopsies of this lesion may be because of the unusual benign histological appearance. With the experience gained from the first case, a positive diagnosis was made by cystoscopic examination and cystectomy was carried out without delay in the second case.

### CASE REPORTS

*Case 1.*—A 20-month-old infant was hospitalized on June 27, 1950, at Georgetown Hospital to determine the cause of repeated urinary tract infections. During this hospitalization there was an episode of gross hematuria. The patient also passed a piece of globular tissue which was subsequently diagnosed as a

Accepted for publication November 4, 1952.

<sup>1</sup> Mostofi, F. K. and Morse, W. H.: Polypoid rhabdomyosarcoma (sarcoma botryoides) of bladder in children. *J. Urol.*, 67: 681, 1952.

<sup>2</sup> Cappell, D. F. and Montgomery, G. L.: On rhabdomyoma and myoblastoma. *J. Path. & Bact.*, 44: 517, 1937.

benign pedunculated fibroma. An excretory urogram revealed a double right kidney and a normal left kidney, but examination of the excretory cystogram showed evidence of multiple filling defects within the bladder (fig. 1).

On July 5, 1950, the patient was admitted to Children's Hospital where physical examination was essentially normal except for bilateral otitis media which rapidly subsided on medication. The white blood count was 28,000 and the urine sediment showed innumerable pus cells and red cells. On July 8, cystoscopy was done and numerous variable sized, translucent, pedunculated polyps having the appearance of a bunch of grapes, were seen on the trigone and vesical neck.

Transurethral resection did not appear to be feasible. Therefore, through a suprapubic cystotomy (fig. 2, A), the polyps and entire thickened mucosa of

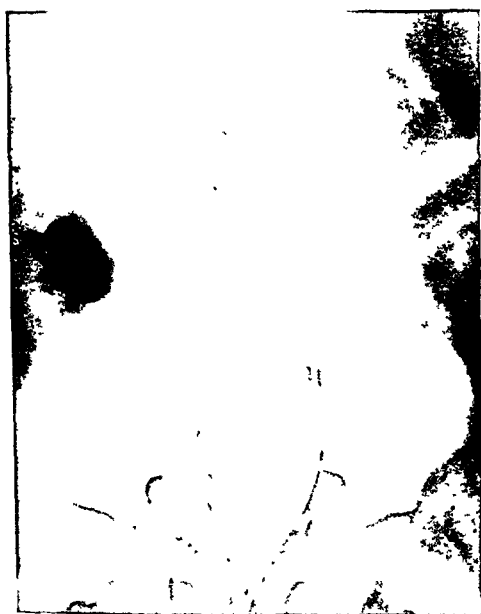


FIG. 1. Case 1 Retrograde pyelogram with ragged filling defects around bladder neck

bladder neck and trigone were excised. The remainder of the polyps were fulgurated. Again the pathological diagnosis was "benign polyps of the bladder."

On January 10, 1951, the child was re-admitted as an emergency case. A large purplish mass of prolapsed polyps completely filling the vaginal orifice and originating from the urethral orifice was present (fig. 2, B). The mass was ligated and the ligature was found later to be on the trigone. On January 24, the polyps were again removed through a suprapubic cystotomy and a transurethral fulguration was repeated. On April 26, a third suprapubic cystostomy was done and the suprapubic tube left in permanently. At this time a preoperative diagnosis of rhabdomyosarcoma was made, but as before, the pathological report was "benign bladder polyp."

After one more prolapse of the tumors through the urethra, it was believed

the condition must be considered malignant in spite of the histological findings. A bilateral modified Coffey 1 ureterosigmoidostomy was done on September 13, 1951. The postoperative course was without incident and on September 25, 1951, total cystectomy was begun. During the procedure, cardiac arrest occurred and cardiac massage was done through a thoracotomy. After several minutes, the heart began to beat regularly. The cystectomy was completed (fig. 3, A). Twelve hours postoperatively the patient died without regaining

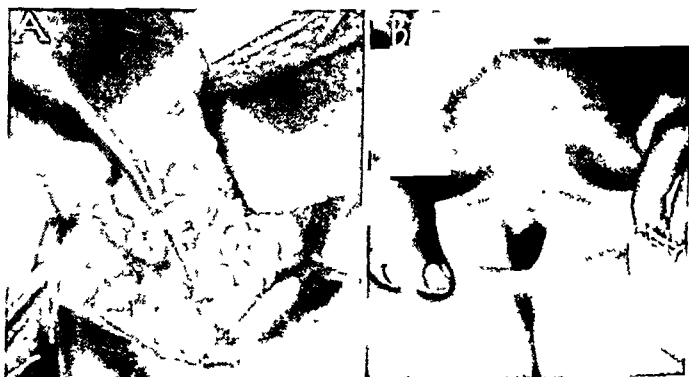


FIG. 2 Case 1 A, open bladder exhibiting polypoid translucent tumor arising from trigone B, polypoid tumor extruding from urethral meatus



FIG. 3 Case 1 A, excised bladder and massive tumor within B, postmortem specimen of left kidney showing metastatic nodule in periphery

consciousness. Autopsy revealed only a single metastatic lesion in the left kidney parenchyma (fig. 3, B). There were no other pertinent findings.

*Case 2.*—A 3-year-old white child was first seen on May 9, 1952, complaining of severe pain and difficulty on urination of 24 hours' duration. She was said to have passed several blood clots that day. Examination of the urine sediment revealed many white blood cells and red blood cells. Excretory urogram, done immediately and without preparation, revealed a normal upper urinary tract, but multiple polypoid, filling defects seen in the bladder were interpreted to indicate that either blood clots or a polypoid sarcoma of the bladder existed (fig. 4).

She was admitted to Walter Reed Army Hospital on May 11, 1952, where physical examination failed to reveal any significant abnormalities. The neonatal and developmental history was also normal. The only childhood disease noted by the parents was German measles. She had absolutely no genito-urinary signs or symptoms prior to the 24 hours before her first visit. Chest x-ray and complete blood count were within normal limits.

Cystoscopy revealed "multiple translucent grapelike polyps arising from the anterior and lateral bladder walls at the bladder neck." Some of the tumors were translucent; others were pink and solid. A gross diagnosis of sarcoma botryoides was made at that time. Bimanual rectal examination failed to reveal



Fig. 4. Case 2. Excretory urogram demonstrating multiple, polypoid filling defects in bladder.

evidence of masses or induration. Examination of the vagina and urethra showed no invasion by tumor.

She was discharged from the hospital to carry out bowel preparation for one week with terramycin .5 gm. daily. The day following re-admission bilateral-ureterosigmoidostomies were carried out, using a modified Coffey 1 technique. The bladder was not opened nor was a biopsy specimen taken since a positive diagnosis had already been made by cystoscopy and cystography. The bladder was removed by the technique described by Millin.<sup>3</sup> After removal, the bladder was opened and an adequate 2 cm. cuff of urethra was seen distal to, and not involved by, the tumor (fig. 4).

The bladder was opened in the anterior midline. In the center of the bladder mucosa there was a large polypoid mass of tiny grapelike structures, elevated 2.5 cm. from the base which measured 5.5 by 3 cm. The surrounding mucosa was smooth and raised above the normal level of bladder mucosa. In the sub-

mucosa there was a gelatinous myxoid material which did not appear to penetrate through the muscularis.

Numerous sections revealed a regular transitional epithelium which suddenly gave way to polypoid masses extending considerably above the level of the regu-



FIG 5 Case 2. Bladder opened in anterior midline showing many translucent polyps arising from broad base

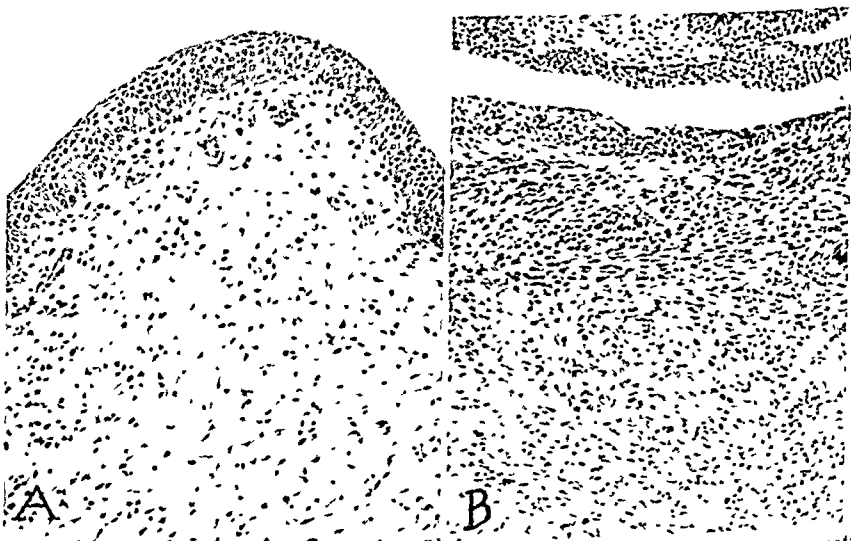


FIG 6 Case 2 Low power photomicrographs. A, showing benign myxomatous nature of tumor. B, showing more cellular area which is still histologically benign.

lar epithelium. These masses were covered by regular, even transitional, epithelium which in some areas approached squamous epithelium. Contained within the polypoid masses, there was a loose, edematous, myxomatous stroma supporting diffusely distributed multipolar stellate cells. These, for the most part, were delicate in appearance. In some areas there were, in addition, crowded

fusiform cells having oval nuclei which contained evenly distributed fine chromatin particles. Mitotic activity was virtually absent. There was a small number of eosinophilic granulocytes. The myxomatous stroma of the polypoid structures did not appear exceptionally malignant, but merged imperceptibly with the normal supporting mesenchymal tissue of the bladder wall. It was difficult to determine, histologically, where tumor and normal mesenchymal structure began (fig. 5). Diagnosis.—Myoma (sarcoma botryoides) of bladder.

The rather stormy postoperative course was marred by a paralytic ileus which, after prolonged gastric suction, was finally relieved.

The plasma bicarbonate level dropped to 13.9 mEq per liter 2 weeks post-operatively and the blood urea nitrogen rose to 34 mg. per 100 cc. The mother was told to add sodium bicarbonate to the patient's food and re-insert the rectal tube at night. The patient was discharged in apparently good health with no outward signs of hyperchloremic acidosis.

#### SUMMARY

Since the only hope for a cure in sarcoma botryoides probably is through early cystectomy, 2 cases have been presented illustrating: a) The diagnosis of sarcoma botryoides can be made by its cystoscopic appearance. b) Biopsy may be misleading since the tumor, in many instances, appears histologically benign.

A plea for uniformity in nomenclature is made to decrease confusion in the literature as well as in the clinician's mind.

1159 Connecticut Ave., Washington 6, D. C. (W.D.J.)

mucosa there was a gelatinous myxoid material which did not appear to penetrate through the muscularis.

Numerous sections revealed a regular transitional epithelium which suddenly gave way to polypoid masses extending considerably above the level of the regu-



FIG. 5. Case 2. Bladder opened in anterior midline showing many translucent polyps arising from broad base.

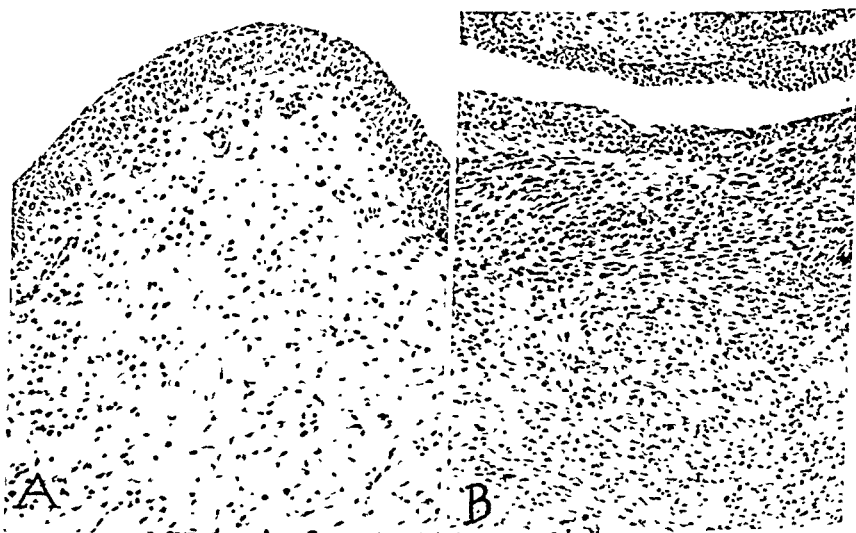


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## MYOSARCOMA OF THE URINARY BLADDER

WILLIAM P. RAMEY, L. L. ASHBURN, HARRY GRABSTALD AND  
JOHN S. HAINES

*From the Urology and Pathology Services of the U. S. Public Health Service Hospital,  
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We wish to report 3 additional cases. Two are leiomyosarcoma while the other case, though not distinguished as to type, is probably a myosarcoma and is one of the longest surviving cases reported.

### CASE REPORTS

*Case 1.* P. D. McC., a 25 year old Negro, was admitted to the hospital April 25, 1950 with complaints of terminal dysuria, nocturia and hematuria of 2 to 3 weeks' duration. Prior to admission he had been treated with sulfonamides with no results. The remainder of the history and physical examination was non-contributory.

The laboratory data revealed a grossly bloody urine with 300 mg./100 cc albumin and a white blood cell count of 13,400 with an essentially normal differential. Hemoglobin, hematocrit and serology were normal.

On cystoscopic examination a tumor was seen measuring about 2 cm. in diameter located on the left side of the roof of the bladder. After complete work-

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The patient returned on August 23, 1950 for repeat cystoscopy. At this time, in the dome of the bladder, a single, isolated, whitish nodule 1 cm. in diameter was seen. A biopsy reported recurrent leiomyosarcoma. On August 29, 1950, segmental resection was performed and the patient made an uneventful recovery to be discharged on the twentieth postoperative day. The excised segment of bladder revealed a 5 mm. ulcerated (previously biopsied) tumor nodule present in the superficial portion of mucosa about 3 cm. from a well healed scar measuring 3 cm. in length. Numerous sections across the line of previous resection did not show tumor.

The patient was examined periodically with no evidence of recurrence until January 17, 1951 (4 months later) when he was admitted to the hospital complaining of a non-tender mass in the right lower quadrant. The mass was firm, semi-fixed, slightly tender to palpation and about 5 cm. in diameter. Cystoscopically, there appeared to be a mass protruding into the bladder lumen from the right lateral side. Biopsy was reported as normal bladder mucosa. It was smooth, hard, and measured 9 by 4 by 4 cm. Covering peritoneum had to be removed with the tumor. The tumor was well circumscribed and its cut surface was gray with scattered small areas of hemorrhage and necrosis.

Postoperatively, a wound abscess developed but healed with appropriate therapy. He was discharged March 17, 1951 but re-admitted March 26 with 2 masses in the lower abdomen. Both were smooth and round: one was estimated to be about 5 to 6 cm. in diameter and the other appeared slightly smaller. Cystoscopically, the right lateral wall of the bladder was seen protruding into the lumen from extrinsic pressure. On x-ray of the chest, a dense shadow was seen in the left lower lobe of the lungs consistent with metastatic tumor. The patient received deep x-ray therapy which was estimated to vary between 2800 and 3900 r. u. to varying parts of the tumor with little or no obvious effect. He was discharged May 24th.

He was admitted for the last time on August 16, 1951 complaining of pain in his right side and leg, dysphagia and constipation. The abdomen was distended and a large tumor was palpated filling the lower abdominal cavity. There was distention of the veins of the upper abdomen. Urinalysis showed hyaline casts. The blood urea nitrogen was 22 mg. per cent: white blood count 3300; and hemoglobin normal. On August 13 the patient complained constantly of abdominal distress and was vomiting brownish foul-smelling material. A few days before death his blood urea nitrogen rose to 163 mg. per cent: the chlorides

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decreased to 83 mEq./l. and the  $\text{CO}_2$  rose to 31 mEq./l. He died August 16, 1951.

**Microscopic examination of surgical specimens:** The primary tumor removed May 4, 1950 was formed for the most part of interlacing fascicles of narrow, spindle-shaped cells, which had picrophilic cytoplasm and slightly hyperchromatic elongated nuclei (fig. 1, A). In a few areas cells were shorter and thick and had nuclei which were large, deeply stained and occasionally lobate. In such areas mitoses were frequent. A few mitoses were seen in the relatively well differentiated spindle-shaped cells. Collagen was abundant centrally and was present but less conspicuous in marginal areas. A few fascicles of bladder muscle

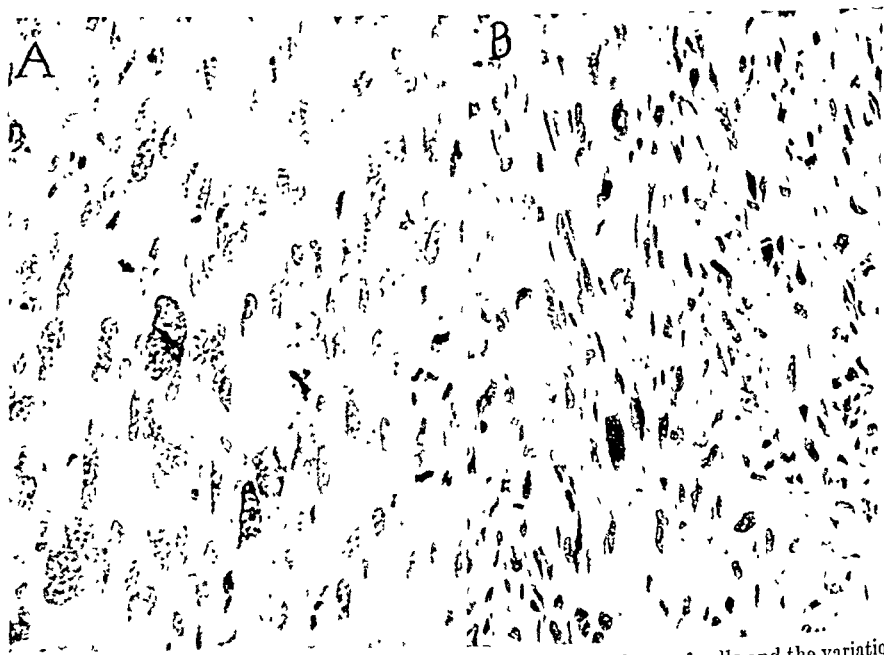


FIG. 1. Case 1. A, primary tumor. Note generally spindle form of cells and the variation in size and staining of nuclei. Mitoses are numerous. One tripolar form is evident.  $\times 300$ . B, pelvic tumor (autopsy specimen) similar to A but showing some nuclear pyknosis and cell fragmentation.  $\times 260$ .

were present within the deep margin of the tumor. Phosphotungstic-acid-hematoxylin stains failed to reveal cross striations. Diagnosis: Leiomyosarcoma.

Microscopic appearances of the biopsy of August 23, the nodule resected August 29, and of the large retroperitoneal tumor removed February 6, were similar in all essential details to the primary tumor. The retroperitoneal tumor, however, showed more frequent mitoses and more numerous cells with lobate or giant nuclei.

**Postmortem examination:** The lower abdomen and pelvis were occupied by two contiguous but separable tumor masses. The pelvic tumor weighed 1900 gm. and was adherent to and partially surrounded the urinary bladder. The posterior and left lateral wall, as well as a portion of the left dome were free of tumor. The left iliac and femoral vessels were surrounded by tumor but were not ob-

structed. There was extension to the right pubic ramus and the psoas muscles. The right ureter was compressed and moderately dilated. The lower abdominal mass was retroperitoneal, weighed 1425 gm., and extended to within 3 cm. of the origin of the superior mesenteric artery. Both kidneys were displaced upward. The terminal ileum was adherent to the tumor and though not invaded was partially obstructed. The cut surface was gray-white and showed a whorled pattern. There was considerable central cystic degeneration of the abdominal mass. Sections through the pelvic mass and bladder showed no evidence of invasion of the muscular portion of the bladder wall. The right kidney pelvis was moderately dilated. Both kidneys were otherwise normal.

The right lung weighed 527 gm. Many tumor nodules up to  $1\frac{1}{2}$  cm. in diameter were scattered throughout, both deep and superficial. The left lung weighed 415 gm. There was a large tumor nodule (6 by 5 by 3 cm.) in the lower lobe. A small (1 cm.) nodule was present in the upper lobe.

The heart, liver, pancreas, adrenals, thyroid, testes, spleen, prostate, brain and bone marrow showed no significant abnormality.

**Microscopic:** The general architecture and cytology of the tumor in the pelvis, abdomen, lungs and mediastinum were similar to that described above for the surgical specimen, the only difference being the fairly extensive necrosis and fibrosis of the abdominal and pelvic tumor and a little more variation in cell and nuclear size (fig. 1, B). Other organs showed no significant pertinent pathologic alteration.

This tumor was studied at the Armed Forces Institute of Pathology and accepted as leiomyosarcoma of the urinary bladder.

**Case 2.** R. E. D., a 70 year old white man, was admitted to the hospital May 30, 1945, on a stretcher, complaining of intermittent hematuria of 3 years' duration and inability to urinate for 3 days.

Examination revealed an elderly chronically ill man. The prostate was moderately enlarged and the bladder distended.

The blood urea nitrogen was 47.9 mg. per cent. An unsuccessful attempt at catheterization necessitated a suprapubic cystostomy. A large diverticulum was observed in the upper left bladder.

The general status improved on catheter drainage; blood urea nitrogen 18.7 mg. per cent after 2 days. On June 19, 1945 cystoscopy was attempted but was unsuccessful because of posterior urethral obstruction. A Foley retention catheter was inserted. Two days later he developed fever and leukocytosis. On July 4, 1945 cystoscopy was performed through the suprapubic fistula and the previously visualized diverticulum was identified as an area suggestive of carcinoma, involving the right bladder wall and adjacent trigone. Biopsy was interpreted as benign epithelial papilloma.

On August 28, 1945, suprapubic cystotomy revealed a spongy friable mass within a 7 cm. diverticulum on the right. Outside the bladder there was considerable induration extending over into the right side of the pelvis. Postoperatively, his course continued down hill and the patient died on November 12, 1945, approximately 6 months after admission.

Postmortem examination: The cystotomy opening exuded a foul-smelling material. The peritoneal cavity contained no fluid and there was no obvious metastatic tumor. The urinary bladder, ureters, both kidneys, and rectum were removed *en masse*. On opening the bladder, a large diffuse friable, necrotic, foul-smelling tumor was noted which appeared to consist of multiple, often confluent nodules of varying size. The non-necrotic tumor was pinkish-gray. On the right bladder wall above the trigone, a diverticulum measuring 4 to 5 cm. in diameter and connected with the urinary bladder cavity by an opening 1 cm. in diameter was noted. The tumor also involved the diverticulum wall. The ureteral openings could not be found. On sectioning the bladder in various areas

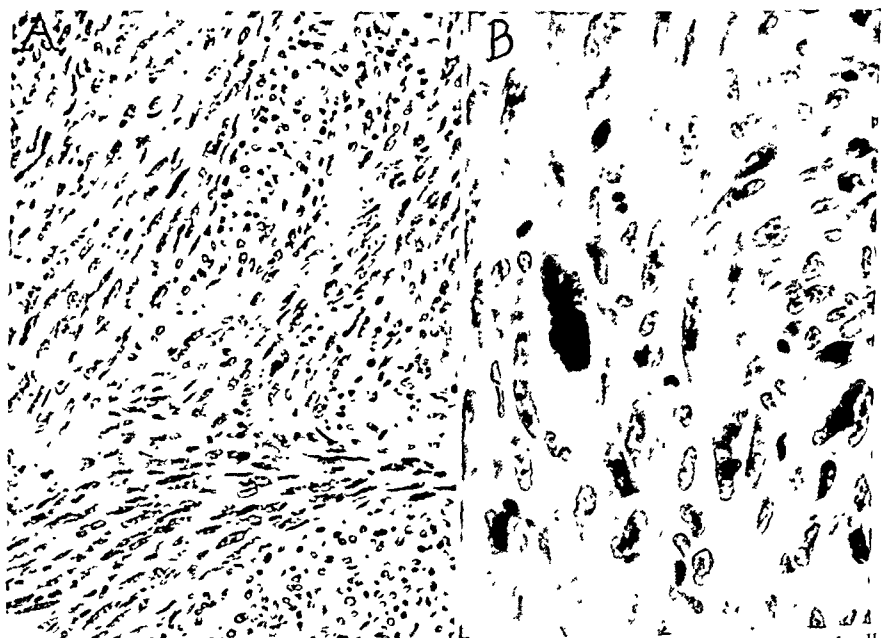


FIG 2 Case 2. A, bladder tumor showing interlacing fascicles of spindle shaped cells  $\times 250$ . B, Area showing variation in cell and nuclear size and form.  $\times 580$ .

the tumor showed extensive involvement of all layers. Both ureters were markedly dilated.

Both kidneys showed marked dilatation of the pelves. The right was filled with a gritty, foul-smelling exudate which lined the mucosal surface. The capsule stripped easily showing a cortical surface presenting scattered soft grayish-yellow areas measuring up to 1 cm. in diameter. There was no evidence of metastases.

Microscopic: The bladder mucosa was replaced and the muscular coat extensively infiltrated by tumor, the cells of which were arranged in intertwining and whirling fascicles. The cells were spindle-shaped and long (fig. 2). Nuclei were also of spindle form, had bluntly rounded ends, a fine reticulated chromatin, occasionally showed small indistinct nucleoli and were not infrequently seen in

mitosis. Though hyperchromatic, most nuclei were of fairly uniform size. In a few areas cells were much enlarged, had bizarre giant nuclei and abundant amphophilic cytoplasm. Stroma was present in minimal amounts, fibrillary in type, and recognized as collagen in the van Gieson preparation. Phosphotungstic acid hematoxylin stains failed to demonstrate cross striations.

The right kidney showed extensive inflammatory changes in the wall of the pelvis extending throughout the medulla and cortex. Similar changes were present in the left kidney, though of minimal extent. Microscopic study of other organs showed no significant pathologic alteration. Diagnosis: Leiomyosarcoma of the urinary bladder with ureteral obstruction; bilateral hydronephrosis and hydro-ureter; pyelonephritis, right and chronic cystitis, severe.

This tumor was studied at the Armed Forces Institute of Pathology and accepted as a leiomyosarcoma of the urinary bladder.

*Case 3.* P. S. H., a 39 year old white woman, was well until approximately November 1938, when she noticed menorrhagia, dysmenorrhea, dysuria, frequency and hematuria. Hematuria had been present for approximately one week. After a urological work-up no cause for the hematuria could be found. A supravaginal hysterectomy was done for leiomyomas of the uterus. Postoperatively, she continued to have hematuria. Further urological study revealed a 3.5 cm. sessile tumor on the right posterior wall of the bladder. Biopsy was reported by the National Institute of Health as myosarcoma (probable leiomyosarcoma). The lesion was treated by fulguration and deep x-ray without success. On February 18, 1939 a suprapubic cystotomy with radium needle implantation was performed. Deep x-ray to a total of 5,000 roentgen units was continued. The patient was well until January, 1940 when she again noticed slight hematuria. Vaginal examination revealed thickening about the bladder base and a mass in apparently the same position as previously noted.

Urinalysis and serology were normal. The white blood count was 4,200 with normal differential. Physical examination was essentially negative except for slight tenderness in the right lower quadrant and the right vaginal fornix. There was no evidence of metastasis and the patient appeared in excellent physical condition. Cystoscopic examination on February 7, 1940, revealed a polypoid tumor about 3 cm. in diameter on the superior wall of the bladder apparently not involving the ureteral orifices.

On February 20, 1940, segmental resection was performed. The 2 cm. tumor appeared in the dome and protruded 1 cm. into the bladder lumen. It was free from both ureters and their orifices. The postoperative course was marred by phlebitis of the right leg and thigh. The patient was discharged from the hospital April 1, 1940 and has been followed periodically for more than 12 years with no recurrences.

*Pathological findings:* The resected bladder segment showed a tumor which had an irregular outline and was sharply circumscribed but not encapsulated. The stroma was fibrous and, in general, slight to moderate in amount though in a few areas it was abundant and hyalinized. Tumor cells varied in form but



were mainly spindle-shaped with long tapering extremities (fig. 3). Nuclei were large, often vesicular and generally had distinct nucleoli. Cytoplasm was oxyphilic and picrophilic, and occasionally showed indistinct, longitudinally arranged fibrillae (phosphotungstic acid hematoxylin stain). Cross striations could not be demonstrated. In the more fibrous areas cells tended to be short and plump. Rarely, very large cytoplasmic masses occurred containing one or two nuclei. Mitoses were rare. This tumor had a basically similar microscopic appearance to that seen in the biopsy specimen removed in 1939. However, the resected specimen showed a more fibrous stroma and tumor cells with more variation in size and form. Diagnosis: Myosarcoma.

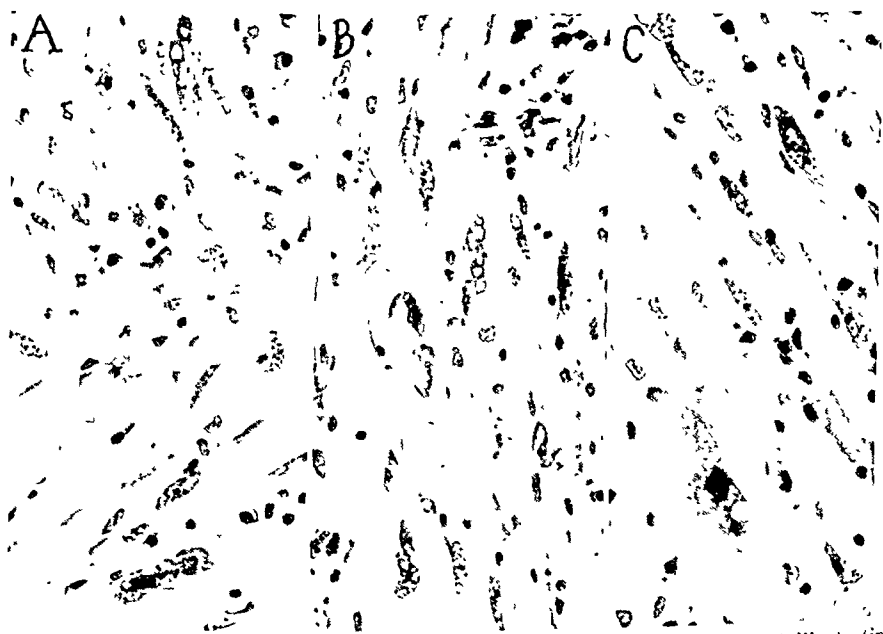


FIG. 3. Case 3. A, B, and C, different areas of tumor (resected specimen) illustrating spindle shaped tumor cells showing considerable variation in nuclear form, size, and intensity of staining. A and B,  $\times 360$ ; C,  $\times 420$ .

This tumor was first studied by the pathology staff of the National Institute of Health. A diagnosis of myosarcoma, probably of smooth muscle type, was made. Dr. Fred W. Stewart of Memorial Hospital, New York City, also classified the tumor as myosarcoma. In view of a 6 year relatively symptom-free follow-up, Dr. Stewart in 1946 was asked again to review the slides. He commented as follows: "This would still have be classed as a myosarcoma; it looks low grade. . . ." In 1950, the opinion of the staff of the Armed Forces Institute of Pathology was expressed as follows: "The majority of the staff considers the lesion as representing a benign process, but the exact nature is difficult to determine. The most likely diagnosis appears to be myo-epithelial hamartoma with secondary inflammation. Other diagnoses include leiomyoma and neurofibroma. However, two members of the staff consider the lesion as leiomyosarcoma."

## COMMENT

Leiomyosarcoma of the urinary bladder is a rare tumor which occurs with about equal frequency in both sexes. The age incidence curve shows two peaks—under 10 and over 50 years.

Hematuria is the most frequent presenting complaint in leiomyosarcoma. However, frequency, urgency, pain and dysuria are also common.

Although this tumor has been reported as occurring in various portions of the bladder, it is most commonly located in the region of the trigone or lateral walls. The topography of the tumor is most often described as sessile, particularly when first observed. If not effectively removed the tumor extends to various portions of the bladder wall and commonly obstructs one or both ureters. Ureteral obstruction, hydronephrosis and suppression of kidney function are the common mechanisms of death. In the few instances in which metastases have occurred the lungs, liver, intestines, and kidneys have been the most frequent site.

Although prognosis is poor in this disease the actual mortality rate is difficult to assess. Of 31 cases reported 10 patients were living and 2 were not stated as to outcome. However, the figure is of relatively little value since in a number of instances the follow-up period was quite short.

Segmental resection or total cystectomy would seem to be the only effective approach to the treatment of this disease. X-ray therapy has been used for local recurrences but without encouraging results.

## SUMMARY

Two cases of leiomyosarcoma of the urinary bladder are reported. One of these occurred in a 25 year old Negro who subsequent to resection of the primary tumor developed local recurrences, metastasis to lungs and died approximately 16 months after onset of symptoms. The second case was in a 70 year old white man who died 6 months after admission to hospital and approximately 3 years following onset of intermittent hematuria. In both of these cases there was ureteral obstruction, hydronephrosis and uremia.

A third case is presented, classified only as myosarcoma, which occurred in a 39 year old white woman. The patient is living and well, approximately 13 years following segmental resection.

Acknowledgment is made to Drs. John Wirth, formerly director of the Tumor Clinic and Homer Skinner, formerly chief of Surgery for permission to publish case Number 3. Dr. H. King Wade of Hot Springs, Arkansas, referred Case 3 to this hospital.

*N. I. H., Clinical Center, Bethesda, Md. (L.L.A.) Crile Veterans Administration Hospital, Cleveland, O. (H.G.)*

## A STUDY OF THE CARCINOGENIC EFFECT OF BETA-NAPHTHYLAMINE ON THE NORMAL AND SUBSTITUTED ISOLATED SIGMOID LOOP BLADDER OF DOGS

W. W. SCOTT AND H. L. BOYD

*From the Department of Surgery, Division of Urology, of the University of Rochester School of Medicine and Dentistry, Rochester, N. Y.*

This study was suggested by the observation that from our clinical experience and knowledge of the literature in cases where ureterosigmoidostomies had been performed because of tumors of the bladder, we were unable to recall a single instance where these growths had occurred in the rectum or sigmoid following the procedure. Hueper, Wiley and Wolfe demonstrated the effectiveness of beta-naphthylamine as a carcinogenic agent upon the normal bladder of the dog and Bisgard, Rubin and Thompson in separate studies have proven satisfactory function with continence following the substitution of the normal bladder of dogs with an isolated loop of the sigmoid into which the ureters had been transplanted. It occurred to us that by combining these two entirely different experimental studies we would have an opportunity to evaluate the action of a carcinogenic agent upon the normal bladder and the isolated sigmoid loop bladder of the dog under similar physiological conditions.

### METHOD

Nine large dogs were selected, and except in one instance, female dogs were used so that regular cystoscopic observations of the bladder could be made. Three dogs were left intact for control purposes. Two other dogs were prepared by diverting the urine from one kidney into the bowel by ureterosigmoidostomy while the opposite ureter was left in its normal position. The left ureter was implanted in one dog and the right ureter in the other. One male and three female dogs, which had been prepared with substituted isolated sigmoid loop bladders and studied by Dr. Thompson, were used. These dogs had remained in a state of good health with perfect urinary control for a period of a year or more following surgery.

The nine animals were first observed for a period of two weeks and noted to be in good health. Preliminary blood urea nitrogen determinations and phenolsulfonphthalein excretion tests which were done on each dog were followed by cystoscopic examinations of the females to determine the absence of bladder pathology. Upon completion of these studies the daily administration of 300 mg. of purified beta-naphthylamine in capsule form was started on all the dogs by mixing the capsule with the regular food ration. The dogs were observed regularly, weighed monthly and cystoscoped at intervals of 3-6 months; blood urea nitrogen determinations were made at the time of each cystoscopic examination.

The dogs were prepared for cystoscopic examinations by anesthesia induced

Read at meeting of Clinical Society of Genito-Urinary Surgeons, Rochester, N. Y. February 5, 1953.

This investigation was supported with funds from the Dr. Henry C. Buswell Memorial.

with nembutal intravenously or intraperitoneally. A 24F cystoscope was introduced into the female urethra without difficulty following dilatation with sounds. Detailed descriptions of the bladders were made at the time of each examination and a biopsy study made if bladder tumors were observed. The beta-naphthylamine was discontinued in some instances because of profuse hematuria and on other occasions to see if any regression occurred in the tumors following withdrawal of the carcinogenic agent.

#### REPORT ON EXPERIMENTAL ANIMALS AND OBSERVATIONS

Dog No. 1, an intact female, first developed bladder lesions after 22 months of beta-naphthylamine administration. These were found in the fundus and appeared as reddened, slightly elevated areas. Beta-naphthylamine was discontinued after 27 months at which time definite edematous polypoid-like tumors were observed. The dog died after 33 months and autopsy revealed bilateral pyonephrosis and hydro-ureter with bilateral obstruction at the ureterovesical junction. The bladder was entirely covered with tumors except the trigone. The individual tumors were pedunculated having small, delicate pedicles which did not appear to infiltrate the bladder wall. For the most part their surface was smooth and edematous in appearance. However in some instances their tips were necrotic. Furthermore an unusual amount of black and purple pigment was present in the tips of many of the growths (fig. 1, *A*). Early biopsy material showed squamous metaplasia while sections obtained from the bladder at autopsy showed areas of well differentiated alveolar type infiltrating carcinoma (fig. 4, *A* and *B*).

Dog No. 2, an intact female, developed numerous papillary tumors in the fundus and around the ureteral orifices after 22 months. Beta-naphthylamine was discontinued at 27 months because of gross hematuria and the sickly appearance of the animal. Death occurred at 28 months. Autopsy revealed obstruction bilaterally at the ureterovesical junction and bilateral pyonephrosis. The entire surface of the bladder, except the trigone, was covered with tumors. This specimen showed many broad-based tumors and thickening of the bladder wall suggesting infiltration (fig. 1, *B*). Microscopic sections showed areas of very anaplastic infiltrating carcinoma and well differentiated squamous carcinoma (fig. 4, *C* and *D*).

Dog No. 3, an intact female, developed numerous papillary growths and also many hemorrhagic areas after 22 months of beta-naphthylamine administration. The lesions were first seen in the fundus but later were noted on both lateral walls. The carcinogenic agent was discontinued after 27½ months in order to observe whether regression of the bladder tumors would occur. Early biopsy studies showed metaplasia of transitional type cells with malignant proliferation into the submucosa. Some sections showed neoplastic cells forming crypts and alveolar spaces lined with squamous epithelium (fig. 3, *D*). The dog is still alive and in a good state of general health after 36 months. No beta-naphthylamine has been administered for a period of 8½ months but we have not observed any regression of the bladder tumors.

Dog No. 4, a female animal with a right ureterosigmoidostomy, was first noted to have bladder tumors at 31 months after the drug was started, at which time the entire bladder was covered except the distal one-half of the trigone. The dog was sacrificed after 32 months of beta-naphthylamine administration. At autopsy both kidneys looked grossly normal but the right ureter was slightly dilated and

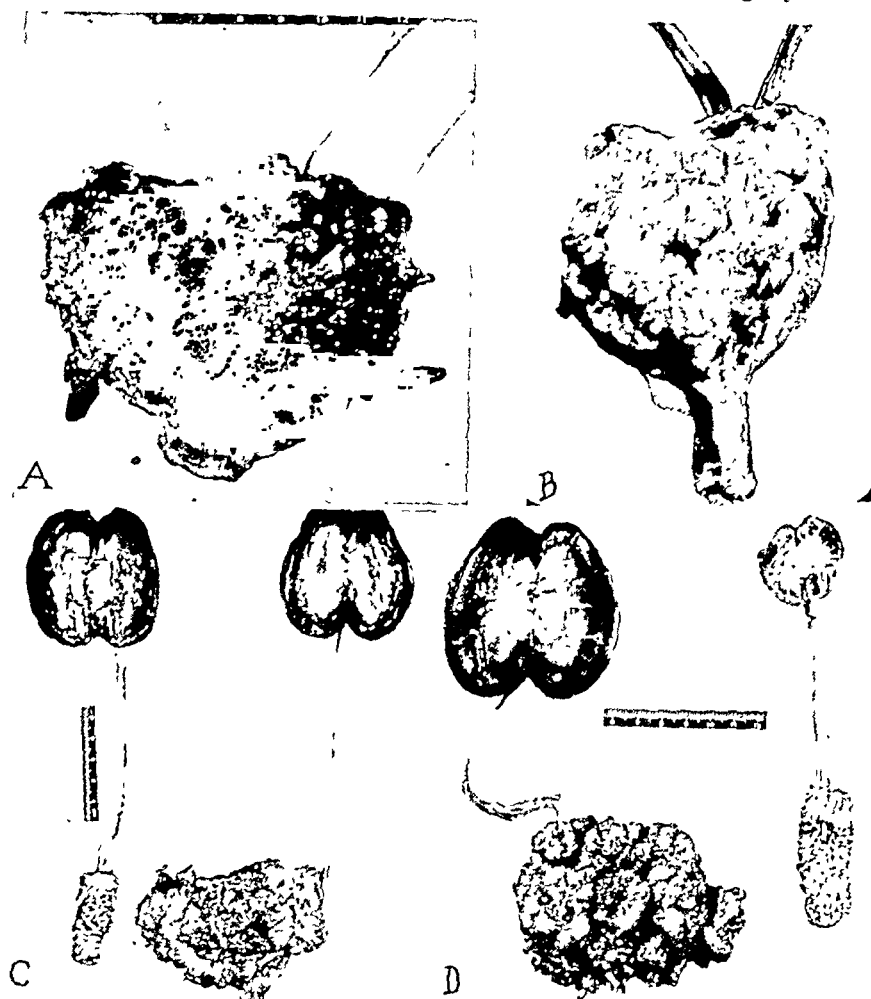


FIG. 1. Tumor growths produced in bladders of control animals by oral administration of beta-naphthylamine. A, dog No. 1, illustrating greatly diversified tumor growth with pedunculated variety predominating. B, dog No. 2, showing sessile type of tumor predominating. C, dog No. 4, note extensive growth in bladder and absence of tumor growth in the bowel in animal with right ureterosigmoidostomy. D, dog No. 5, showing specimen with left ureterosigmoidostomy and result similar to that of C.

thickened. The ureter, at the site of the ureterosigmoidostomy was patent but strictured. Neither at the site of ureteral transplant nor elsewhere was there tumor growth in the bowel. The bladder showed innumerable growths, both polypoid and papillary, but in this specimen the papillary tumors, of the type shown in figure 2, predominated, the specimen appearing very much like extensive

papillary carcinoma as seen in the human (fig. 1, C). Sections from the right ureter and kidney pelvis revealed early neoplastic proliferation of transitional cells very similar to some of the early changes observed in the bladders (fig. 6).

Dog No. 5, a female animal with a left ureterosigmoidostomy, first developed tumors after 24 months of drug administration. A study of biopsy material obtained cystoscopically revealed early neoplastic proliferation of the squamous cell type (fig. 3, C). While growths were first noted in the fundus the entire bladder later became covered. Beta-naphthylamine was discontinued at 24 months because of gross hematuria and because the bladder tumors were well estab-

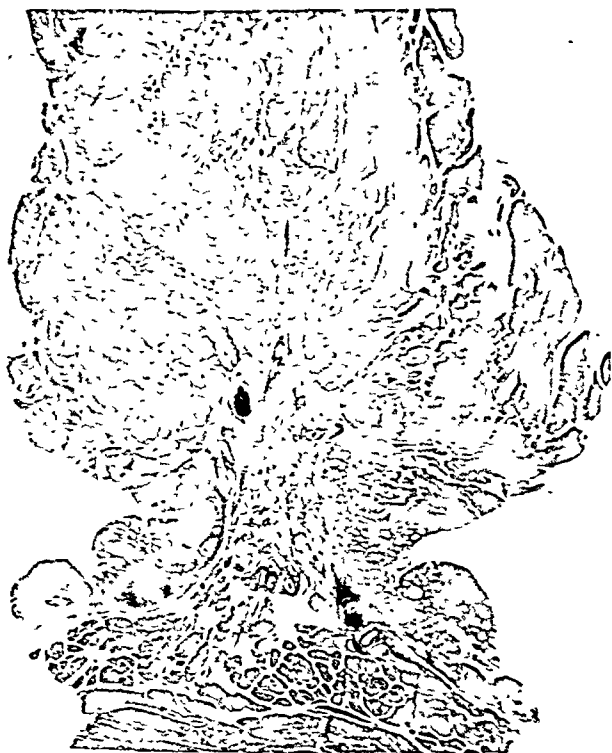


Fig 2 Dog No. 4 Low power section of typical papillary carcinoma of bladder

lished. The dog remained in good health but was sacrificed at 32 months. At autopsy the right kidney appeared normal while the left was completely atrophic. Both ureters appeared normal. The bladder was filled with tumors which were predominantly papillary in character (fig. 1, D). Microscopic sections revealed papillary carcinoma with infiltration through the entire bladder wall. Regression of the bladder tumors did not occur after the administration of beta-naphthylamine was discontinued.

Dog No. 6, a female animal prepared with substituted isolated sigmoid loop bladder, did not develop bladder tumors. The dog became ill at  $26\frac{1}{2}$  months so beta-naphthylamine was discontinued. Hematuria developed 2 months

later but no bladder tumors were observed cystoscopically. Death occurred at 31½ months and autopsy revealed a ruptured pyonephrotic right kidney. The bladder, left ureter and kidney appeared grossly normal. An obstructing, indurated mass was present in the lower end of the right ureter (fig. 7, A). Study

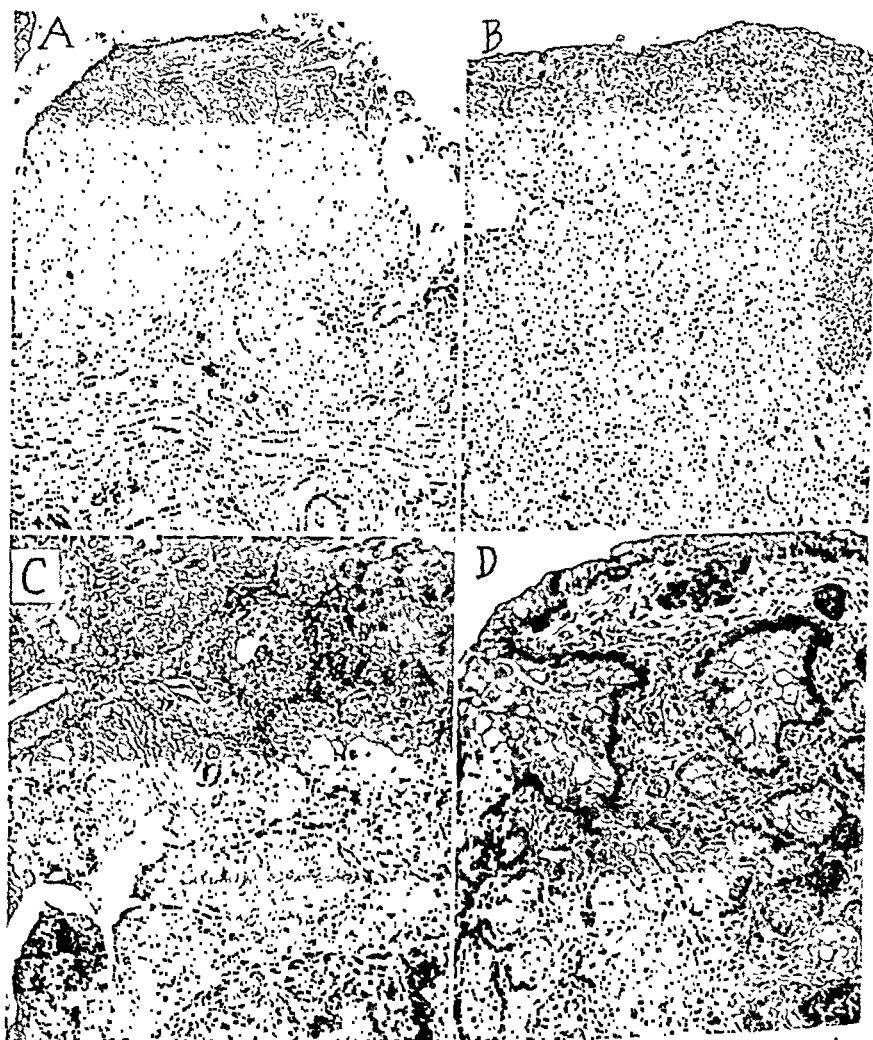


FIG. 3. Early neoplastic proliferative changes observed in bladders of control series. A, dog No. 4, section showing transitional type of cell proliferation but with no definite invasion. B, dog No. 4, section demonstrating greater neoplastic proliferation of transitional type cells. The section showed invasion into sub-epithelial layer. C, dog No. 5, section in which there was early neoplastic proliferation showing squamous type of cells. D, dog No. 3, section demonstrating neoplastic cells forming crypts and alveolar spaces lined with squamous epithelium.

of microscopic sections from this mass showed carcinoma of the ureter of squamous cell type invading muscle (fig. 7, B).

Dog No. 7, a female animal prepared with substituted isolated sigmoid loop bladder, did not develop bladder tumors but died after 31 months of beta-

naphthylamine administration. At autopsy the right kidney and ureter appeared normal but the left kidney was greatly enlarged and pyonephrotic. An obstructing mass was present just below the ureteropelvic junction (fig. 8. A). Study of

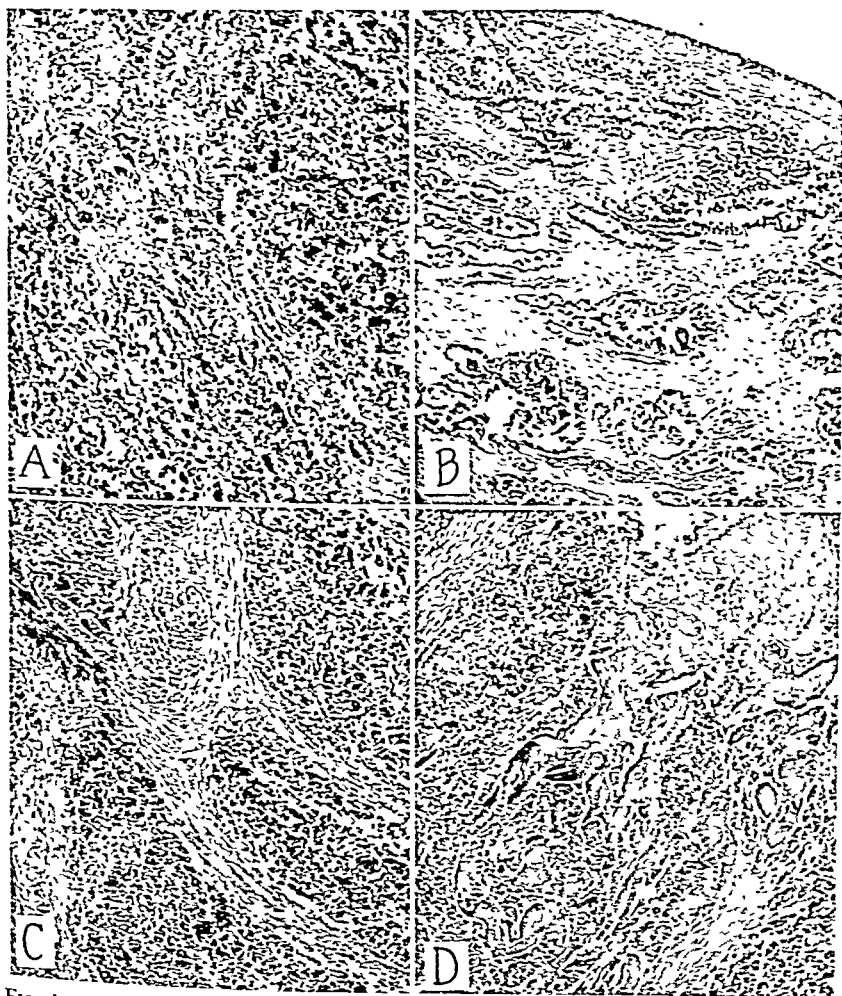


FIG 4. Anaplastic invasive changes found in the intact dog bladders. A, dog No 1, section showing a very anaplastic epithelial growth forming alveolar-like spaces. B, dog No 1, illustrating a slight variation of the anaplastic alveolar type carcinoma shown in A. C, dog No. 2, showing highly anaplastic invasive tumor involving muscle. D, dog No 2, carcinoma showing areas of well differentiated squamous cells and anaplastic cells.

microscopic sections from this mass revealed an invasive undifferentiated carcinoma of the ureter (fig. 8. B).

Dog. No. 8, a male animal prepared with substituted isolated sigmoid loop bladder, remained in excellent health during  $33\frac{1}{2}$  months of beta-naphthylamine administration. Autopsy at the time the dog was sacrificed revealed normal



kidneys and ureters. The artificial bladder had the appearance of normal bowel wall both grossly and microscopically (fig. 5).

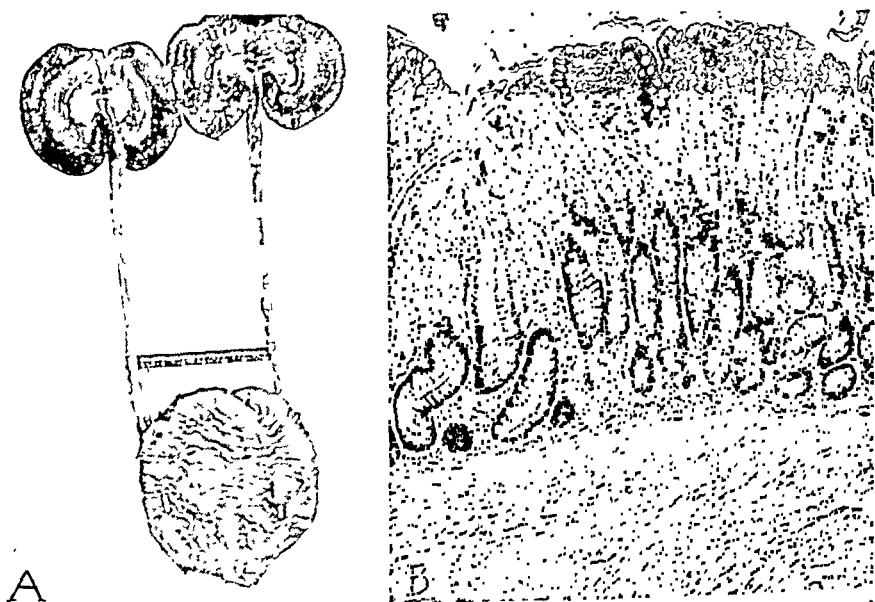


FIG. 5. Dog No. 8. *A*, normal appearing sigmoid loop bladder, ureters and kidneys after 33½ months exposure to carcinogenic agent. *B*, note normal appearance of section from the sigmoid loop bladder.

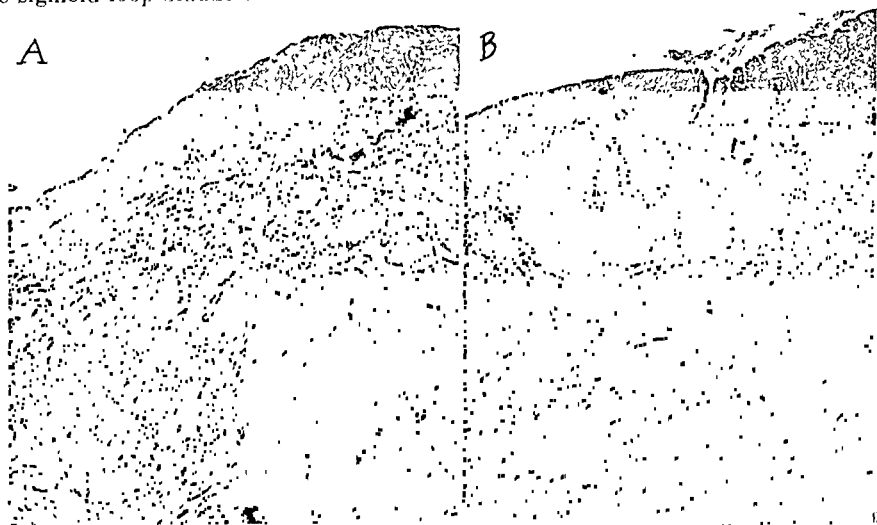


FIG. 6. Dog No. 4. *A*, early neoplastic proliferative changes occurring in the right ureter secondary to stricture at site of uretersigmoidostomy (fig. 1, *C*). *B*, section taken from kidney pelvis of the same specimen which is quite similar to bladder section shown in figure 3, *A*.

Dog No. 9, a female animal prepared with substituted isolated sigmoid loop bladder, is still alive and in good health after 35 months of beta-naphthylamine administration. No bladder tumors have been observed at regular cystoscopic examinations.

In the early stages of the experiment the dogs showed no ill effects from the beta-naphthylamine but later hematuria usually occurred at about the time the first tumors were noted. The blood urea nitrogen determinations showed only

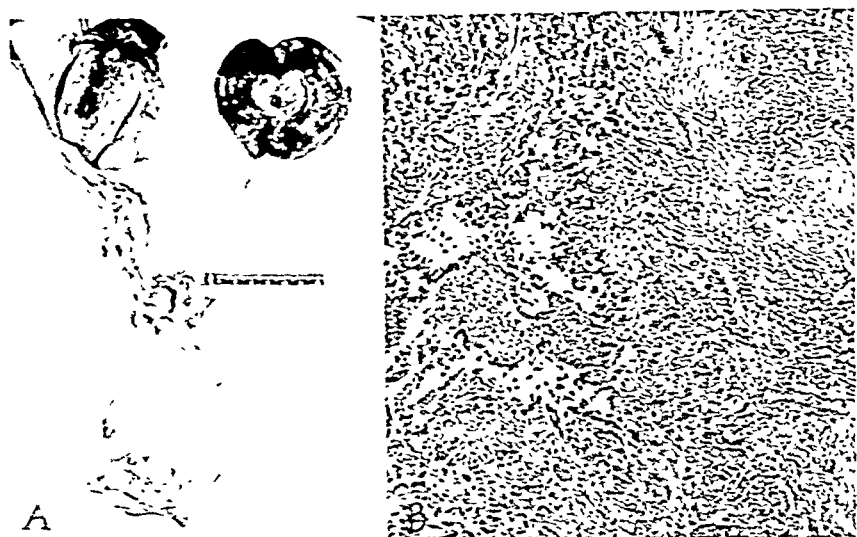


FIG. 7. Dog No. 6. A, uninvolved sigmoid loop bladder with carcinoma in lower third of obstructed right ureter. B, section of carcinoma of right ureter showing squamous type cells invading muscle.



FIG. 5. Dog No. 7. A, gross specimen showing uninvolved artificial bladder and carcinoma in upper third of left ureter. B, section of more undifferentiated type of invasive carcinoma than shown in figure 7. B.

slight variations within normal limits and, while minor fluctuations in weight were noted, most of the dogs gained during the experiment.

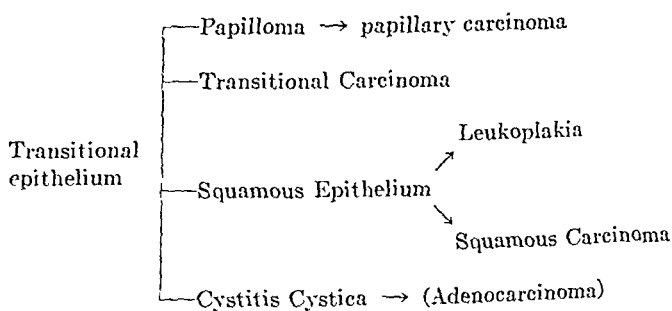
All the animals with intact bladder developed tumor within a period of 22-31 months, the responses being similar to the findings of Hueper, Wiley and Wolie. The early tumors were invariably multiple and seen in the most dependent por-

tion of the bladder, that is, high in the fundus anteriorly, posteriorly and laterally. Later the bladder wall became diffusely covered by tumor with no sites of predilection. The region of the ureteral orifices was usually involved late while the trigone was free from tumor in three of the five bladders in which tumors were produced.

On cystoscopic examination the early lesions appeared to fall into three distinctly different patterns. In several instances small papillary tumors with delicate villi were noted, some being pedunculated while others were sessile. A more common type of early lesion was a smooth, edematous appearing polypoid growth which was pink in color during the early stages but later became reddish or purple. A third type of early lesion was a small hyperemic area appearing flat or slightly elevated which disappeared later or remained to develop into one of the types of tumors described above.

During the latter period of the experiment the bladders became almost completely filled with tumors which varied considerably in their appearance and which were either pedunculated or sessile in character. The pedunculated tumors were of two distinct types; some were smooth, edematous, polypoid lesions while others were more irregular and friable with short fused, red villi similar to the papillary carcinoma seen in the human. Most of these pedunculated tumors appeared to arise from thin stalks which showed no gross evidence of infiltration, but some had bases of greater diameter with apparent infiltration into the bladder wall. The sessile tumors remained flat or slightly elevated, were usually smooth and firm and in many instances appeared infiltrating in character.

Microscopic studies revealed that we had produced practically all of the changes observed in the transitional epithelium of the human bladder and to a lesser degree in the upper urinary tract.\* In brief, these changes are shown in the diagram below.



The earliest cell change noted in the transitional epithelium was a proliferation of cells with increase in the thickness of the mucosa. With further proliferation the cells invaded the submucosal tissue and muscle. In some of the early biopsy specimens squamous metaplasia was noted and others showed nests of cells and alveolar spaces with intact overlying mucosa (fig. 3). There were areas

\* We are very grateful to Dr. William B. Hawkins of the Department of Pathology for his invaluable aid in classifying and describing the different types of tumors observed in this study.

where tongues and crypts of cells could be seen passing into the subepithelial layer, suggesting how these nests and alveolar spaces may be formed. The microscopic pathology seen in the well established tumors varied a great deal. Most of the large papillary tumors showed histological characteristics of papillary carcinoma although some benign papillary structures were seen. The large polypoid tumors showed a well differentiated alveolar type carcinoma. Very anaplastic infiltrating transitional cell growths were common and some of these showed areas of well differentiated squamous carcinoma (fig. 4). There were numerous instances where the tumors had infiltrated deeply into the musculature of the bladder wall. Autopsy study of dogs No. 4 and 5 revealed no tumor of the bowel where ureterosigmoidostomy had been done but in dog No. 4 study of the microscopic sections of the right ureter and kidney pelvis showed areas of beginning neoplastic proliferation of the transitional cells quite like the changes repeatedly observed in the bladder (fig. 6).

The four dogs prepared with substituted isolated sigmoid loop bladders were fed 300 mg. beta-naphthylamine daily for periods of 26½–35 months. It is noteworthy that the bladders of this group of dogs continued to secrete large amounts of mucus and at the time of cystoscopic examinations mucus was invariably seen clinging to the bladder wall. At no time was a bladder tumor observed cystoscopically or at autopsy in this group. One animal, dog No. 8, was sacrificed after 33½ months of beta-naphthylamine administration. No disease was found in the kidneys or ureters and the substituted isolated sigmoid loop bladder, which had been in use for a period of approximately four years, was indistinguishable from normal bowel wall (fig. 5). The administration of the beta-naphthylamine to dog No. 6 had to be discontinued after 26½ months because it lost weight and looked sick. Hematuria was observed 2 months later although no bladder tumor was present. The explanation for this was revealed at autopsy where a hard tumor mass was found just above the ureterovesical junction on the right side causing a widely dilated right ureter and a pyonephrotic kidney. Study of the pathological sections from the mass revealed carcinoma of the ureter (fig. 7). Dog No. 7 died of a large pyonephrotic left kidney, secondary to an indurated mass involving and obstructing the left ureter just below the ureteropelvic junction. Study of the sections from this area revealed carcinoma of the ureter (fig. 8). Dog No. 9 has remained alive and well over a period of 35 months and no tumor has been observed.

#### DISCUSSION

By the method employed in this experiment we have been able to produce carcinoma of the bladder in all dogs with an intact normal bladder. These tumors, which appeared in 22–31 months, were seen first in the most dependent portion of the bladder and varied a great deal in gross and microscopic pathology. The first appearance of tumors in the dependent portion of the bladder suggests that the development of bladder tumors, in both man and dog, may be greatly influenced by the degree of concentration and the time of exposure of this type of

tissue to the carcinogenic agent. Although infiltration deep into the bladder wall was observed, no perivesical extension was noted and no distant metastases were observed. Once the tumors were well established, withdrawal of the carcinogenic agent had no apparent retarding effect upon them.

As far as we were able to determine from a review of the literature, we have been able to produce for the first time, by means of a known carcinogenic agent, early proliferative neoplastic lesions of the ureter and kidney pelvis and primary cancer of the ureter. The lesions of the ureter and renal pelvis were observed after 32 months of beta-naphthylamine administration in a dog where stasis followed a right ureterosigmoidostomy. In each instance of primary carcinoma of the ureter the tumor was discovered approximately 31 months after the administration of the drug was started and occurred where stasis had followed the implantation of the ureter into the isolated sigmoid loop bladder. It would therefore seem that in the presence of a carcinogenic agent, stasis might well be a contributing factor in the development of primary carcinomas of the ureter and renal pelvis.

Inasmuch as tumors did not develop in the substituted isolated sigmoid loop bladders when exposed to the same carcinogenic agent under similar functional conditions and over a longer period of time than that necessary to cause new growths in the normal bladder of dogs it would seem that the absence of tumor growth in the bowel following ureterosigmoidostomy for bladder tumors could not be explained by the presence of fecal material alone. There is a possibility that the secretion from the mucus glands prevented contact of the carcinogenic agent with the epithelium or, in some way, counteracted or destroyed its effectiveness. With the hope of obtaining further information concerning the possible anticarcinogenic action of the mucus secretion, a section of the sigmoid colon has been transplanted into the bladders of a series of dogs receiving beta-naphthylamine. It is also quite possible that this particular carcinogenic agent is incapable of causing the development of new growths of the sigmoid mucosa.

#### CONCLUSIONS

In confirming the findings of Hueper, Wiley, and Wolfe, we have further observed that under the stimulus of the carcinogen beta-naphthylamine we have produced practically all types of epithelial bladder tumors common to man.

For the first time we have reported the production of primary carcinoma of the ureter in two instances and the appearance of early neoplastic proliferative changes of the renal pelvis and ureter in another, in dogs receiving beta-naphthylamine.

We have been unable to produce neoplastic vesical lesions in four dogs prepared with substituted isolated sigmoid loop bladders.

Possible reasons for the absence of bladder tumors in the substituted isolated sigmoid loop bladders and for the finding of carcinoma of the ureter in two instances have been discussed.

Further studies on carcinoma of the bladder in the dog have been started as a result of the above observations.

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## NITROFURAZONE IN THE TREATMENT OF NONSPECIFIC URETHRITIS IN WOMEN

VERNON H. YOUNGBLOOD

*From the Surgical Service (Urology), Cabarrus Memorial Hospital, Concord, N. C.*

Nonspecific, or granular, urethritis is a common finding in women. One only has to keep in mind the possibility of its occurrence, use the panendoscope freely, and he will be rewarded with an increasing number of positive diagnoses.

The normal urethra closely resembles in appearance the bladder epithelium. The male prostatic urethra in chronic prostatitis has a characteristic semblance; nonspecific urethritis in women looks similar. The urethra has increased folds, dilated and tortuous blood vessels that easily bleed, an edema that frequently has granulation tissue superimposed, and polyps. There is no one characteristic appearance, but experience in observation, as in all endoscopic work, is necessary to grade the degree and variations of irritation.

The symptoms are: frequency, urgency, dysuria, nocturia, incontinence, straining, sense of incomplete emptying, and frequently the patient will say that it is an effort to void. If a man would have any of these symptoms, we would unhesitatingly look first to the urethra as the source of trouble. The same applies to women.

The urinary findings are variable, but usually the microscopic examination is negative.

The standard treatment over the years has been urethral dilatations and applications of a silver compound. Attention has been directed to foci of infection, particularly in the female genital tract. Irritating foods are usually withheld. Systemic therapy per se has usually been futile. Under this regimen, improvement can be expected in 6 to 8 weeks.

Over the last year, a new treatment has been used. This came about following discouraging results from the dilatation and silver nitrate treatment. Furacin brand (Eaton Laboratories, Inc.) of nitrofurazone has been used by me almost exclusively over the past 2½ years as an instillation in the bladder for cystitis. When used in a dilution of 1:10 in saline, it has been nonirritating and highly effective. As a result of its effectiveness in cystitis, silver compounds, acriflavine, potassium permanganate and others have been abandoned. However, Furacin solution instilled into the bladder, though effective in urethritis, was not completely satisfactory. Direct applications were then made to the urethra, and this method of application is the basis for this report.

Furacin is an antibacterial agent with high potency in high dilutions. This nitrofurazone compound has been proved by others to be bactericidal to most all common organisms found in the urinary tract, in much greater dilution than the 1:500 strength used as described below. A notable exception, however, is *Proteus*.

The method of use at first was the application of Furacin soluble dressing on a cotton applicator to the urethra. The patient was then taught to insert the appli-

cator herself, two times each day, following a sitz bath. The patient was placed on forced fluids with restriction of irritating foods and drinks such as carbonated drinks, alcohol, citrus juices, etc. The vagina was routinely examined, and where treatment was needed, it was prescribed. Bladder or renal abnormalities were treated when present. If a urethral stricture was present, dilatations were done.

From April 24, 1952 to October 1, 1952, the diagnosis of nonspecific urethritis was made 94 times. Of this number, forty were sufficiently studied and followed for satisfactory analysis. Many others stated they were symptom-free and believed that they needed no further treatment. Not included in this survey, but included in the total number of diagnoses, were 2 cases of urethral diverticulum, 1 case of hypertrophy of the para-urethral glands with urinary retention, and 6 cases whose other renal or bladder abnormalities overshadowed the urethritis and in whom urethritis was more or less incidental. Diabetes was associated in 1 case, chorio-epithelioma in another. The cases in this survey were treated in the office. The symptoms (many had multiple symptoms) were:

|                                                     | Cases | Per Cent |
|-----------------------------------------------------|-------|----------|
| Frequency                                           | 36    | (90)     |
| Dysuria                                             | 30    | (75)     |
| Urgency                                             | 27    | (68)     |
| Nocturia                                            | 26    | (65)     |
| Difficulty in initiating and passing urinary stream | 26    | (65)     |
| Stress incontinence                                 | 4     | (10)     |
| Urgency incontinence                                | 1     | (3)      |
| Pain in abdomen                                     | 4     | (10)     |
| Backache                                            | 1     | (3)      |
| Pressure in bladder                                 | 1     | (3)      |
| Pain in lower abdominal quadrant (localized)        | 1     | (3)      |
| Pain in hips and thighs                             | 1     | (3)      |

The duration of symptoms varied from 1 day to 18 years. Seven patients had symptoms for one or more years, eleven had symptoms from 1 to 12 months, fourteen from 1 to 4 weeks, and eight from 1 to 7 days. The urinary findings were:

|                                                  | Cases | Per cent |
|--------------------------------------------------|-------|----------|
| Normal                                           | 26    | (65)     |
| Occasional to 1-2 RBC per high power field       | 6     | (15)     |
| Occasional to 1-2 pus cells per high power field | 2     | (5)      |
| Innumerable pus cells                            | 2     | (5)      |
| Positive sugar                                   | 1     | (3)      |

Urine cultures showed no growth in 22, unidentified streptococcus, 2; Streptococcus viridans, 2; non-hemolytic gram positive micrococci, 4; spore-forming bacilli, 4; Proteus, 4; non-hemolytic streptococcus, 4; and coliform, 6. An interesting finding, but not accurately tabulated, was the presence of mucus on microscopic examination. This was not looked for but because of its frequent presence became quite prominent.

The urethral changes were graded as to degree of irritation:

|                                                       | Cases | Per cent |
|-------------------------------------------------------|-------|----------|
| Minimal                                               | 1     | (3)      |
| Moderate                                              | 11    | (27)     |
| Marked (urethral stricture was present in four cases) | 28    | (70)     |



Bladder findings were:

|                 | <i>Cases</i> | <i>Per cent</i> |
|-----------------|--------------|-----------------|
| Normal          | 20           | (50)            |
| Trigonitis      | 13           | (33)            |
| Cystocele       | 3            | (8)             |
| Acute cystitis. | 2            | (5)             |
| Caruncle        | 3            | (8)             |

The upper urinary tract was studied in thirteen cases. The findings were:

|                                       |    |
|---------------------------------------|----|
| Kidney stone                          | 2  |
| Ureteral stone (also had renal stone) | 1  |
| Stricture of ureter, postoperative    | 1  |
| Negative                              | 10 |
| Not studied                           | 27 |

Furacin was applied to the urethra two times daily but occasionally, when symptoms had nearly disappeared, once daily. After this study started, the makers of Furacin kindly supplied a new dosage form, Furacin urethral suppositories. This made the drug much easier to administer and no patient had more than minimal difficulty in its use. These suppositories contain Furacin 0.2 per cent with the topical anesthetic, dipherodon hydrochloride 2 per cent in a water dispersible base. The length of treatment was:

|          |                       |
|----------|-----------------------|
| 1 week   | 16 cases              |
| 10 days  | 3 cases               |
| 2 weeks  | 18 cases              |
| 3 weeks  | 1 case                |
| 4 weeks  | 1 case                |
| 5 months | 1 case intermittently |

(2 patients had repeated courses of treatment; one, 1 week; one, 2 weeks)

Furacin solution N. N. R. in a 1:10 dilution of stock drug was instilled into the bladder at each weekly office visit thereafter. Sitz baths were prescribed with the urethral applications.

The results showed that twenty-eight were entirely symptom free at the end of the treatment and twelve improved. Many of the patients who were improved probably could have been termed cured had they been seen again. The urethra by endoscopic examination in every case was improved, though there was no close parallelism with the symptoms. In other words, the patients became symptom-free before the endoscopic findings were normal or stationary. One patient was treated for 3 months with only moderate improvement; she has been advised to have a marked cysto-urethrocele and old perineal laceration repaired. Another patient did not improve until Banthine was used in association with the Furacin treatment.

#### DISCUSSION

Burns and Butt, in describing their results with chronic urethritis using bladder irrigations, sounds, and silver nitrate to the urethra, found complete relief of symptoms in 90 per cent in 6 to 8 weeks. Spence used the same treatment in

half of his cases and electrocoagulation in about half. He does not give the time for improvement but infers a period of treatment of about 4 to 6 weeks or longer.

The treatment described using Furacin requires a minimum of office visits, does away with the pain of urethral dilatations and silver nitrate applications. Symptomatic improvement has been noticed as early as 1 day after beginning treatment, and the average period of treatment is 13 days. The patient can easily use the medication at home herself.

#### SUMMARY

The use of Furacin urethral suppositories in the treatment of nonspecific urethritis in women has been presented. The treatment period is shorter and more comfortable than with the conventional method of sounds and silver preparations.

#### ADDENDUM

Since the paper was submitted, more than 300 additional cases of urethritis have been treated with Furacin urethral suppositories. The findings in these cases have been parallel to the ones discussed above. One case of urethral diverticulum and 2 cases of aberrant ureteral orifices have been found. Three cases of sensitivity to the medication have also occurred. This has not been manifested on the endoscopic findings but in each case has been vulval irritation. All cases responded to discontinuance of the drug and local applications of pyribenzamine ointment. Several cases of urethritis in men that have been refractory to all other treatment have improved with Furacin urethral suppositories.

The suppository method of medication has proved its worth. Several cases of marked granular changes in the urethra have not responded to Furacin urethral suppositories. These have responded slowly to the old treatment of that of 10 per cent silver nitrate applications to the urethra. With this in mind, silver nitrate suppositories are now in the process of manufacture for clinical trial.

*Kannapolis Highway, Concord, N. C.*

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## A FURTHER CLINICAL AND PATHOLOGICAL STUDY OF PROSTATIC INFARCTION

MANO R. GOLDEN AND B. S. ABESHOUSE

*From the Department of Urology, Sinai Hospital, Baltimore, Md.*

Since the first report of 3 cases of prostatic infarction by Abeshouse in 1933, the addition of over 300 cases to the literature by other authors has firmly established this pathological entity. However, the etiology, pathogenesis, and significance of this condition and a concomitant finding, so-called squamous metaplasia, remain controversial. This present work is a study of 70 cases of infarct of the prostate seen in this clinic.

### MATERIALS

The specimens in this study were obtained surgically by all the methods of prostatectomy. The sections taken from each specimen varied in number up to 12. No operative specimens were cut serially. A standard hematoxylin and eosin stain was employed. The criterion for the presence of an infarct in the prostate was the microscopic observation of an actual infarct. Lesions described as healed infarcts or so-called squamous metaplasia alone were not included.

### INCIDENCE

In a large necropsy series, Moore found 170 cases (25 per cent) of prostatic infarction in 680 cases of benign prostatic hypertrophy. His high figure may be due to the inclusion of the "healed infarct," which he recognized as an ovoid or round area in which special stains demonstrated the presence of only connective tissue with islands of epithelium. Baird, McKay, and Kimmelstiel reported 66 cases (18.7 per cent) of prostatic infarct in 352 surgically enucleated specimens. They did not include ovoid or round areas devoid of muscle tissue. Sutton and McDonald found 30 (13.6 per cent) infarcts in 220 operated cases, Roth 18 (8 per cent) in 220 cases. Hubly and Thompson reported 10 cases, Culp 9, Rogers 2, and others additional individual cases. The 70 cases (10.3 per cent) in this study were obtained in a series of 679 prostatectomies.

Moore reported the maximum incidence of clinical symptoms of urinary obstruction was present at 65 years of age (table 1). The average age in this study was 69 years, indicating that infarct of the prostate occurs at a later age than that of the average prostatic patient seeking relief.

### CLINICAL FINDINGS

Pain is a frequent finding in infarction elsewhere in the body. None of the 70 patients had any usual pain other than that associated with voiding. Pyuria was present in 14 (20 per cent) and leukocytosis in 16 (23 per cent) of the cases. One patient had syphilis and 9 had a past history of gonorrhea. In the series of

Read at annual meeting, Mid-Atlantic Section, American Urological Association, Philadelphia, Pa., April 18, 1952.

Baird, McKay, and Kimmelstiel a history of previous urinary retention was four times greater in those cases of benign hypertrophy of the prostate with infarcts than in those cases without infarcts; while acute urinary retention was three times greater in the former variety. The incidence of hematuria was twice as great in cases with infarcts. Hubly and Thompson maintained that swelling of the infarct may cause obstructive symptoms and that cicatrization relieved obstruction. In fact, they postulated that "if the infarct is large, prostatectomy may take place automatically." Rogers had 2 cases he felt had obstructive symptoms due to infarct with acute swelling which apparently subsided thereafter. In the authors' series of 70 cases, acute urinary retention was present in 51 (73 per cent) and gross hematuria in 26 (37 per cent). As might be expected in this age group, 42 (60 per cent) patients had arteriosclerotic and/or hypertensive cardiovascular disease. Diabetes was present 3 times, marked azotemia 4 and hernia 7 times. There were 14 (20 per cent) instances of calculi: 9 in the bladder, 3 in the prostate, 1 in the ureter and 1 in the kidney. Other conditions observed

TABLE 1. *Age*

| <i>Years</i> | <i>Cases</i> | <i>Years</i> | <i>Cases</i> |
|--------------|--------------|--------------|--------------|
| 45-49        | 1            | 70-79        | 21           |
| 50-59        | 9            | 80-89        | 6            |
| 60-69        | 33           |              |              |

TABLE 2. *Operation*

|                                  |    |
|----------------------------------|----|
| 2 stage suprapubic prostatectomy | 28 |
| 1 stage suprapubic prostatectomy | 20 |
| Perineal prostatectomy           | 15 |
| Retropubic prostatectomy         | 4  |
| Transurethral resection          | 3  |
| Bilateral partial vasectomy      | 69 |

in single cases were bladder papilloma, carcinoma of the bladder in a diverticulum, cholelithiasis, and gangrene of the foot.

All 70 patients were examined cystoscopically before operation. In no case was it possible to visualize or diagnose the prostatic infarction by cystoscopic examination, as has been reported by Hubly and Thompson who described a bluish tinge in the urethra.

The type of operation performed in the authors' series is indicated in table 2.

#### POSTOPERATIVE COMPLICATIONS

Four (5.7 per cent) patients died after operation. Three had a 2 stage suprapubic prostatectomy; viz: the first was 88 years old and died of anuria; the second was 68 years old and died of shock and pyelonephritis; and the third was 78 years old and died of myocardial insufficiency. The fourth patient had a perineal prostatectomy and succumbed following an acute myocardial infarction. Complications seen in the other patients were pyelonephritis in 6 cases, shock in 6, thrombophlebitis in 2, pneumonia in 2, and hemorrhage, incarcerated hernia, urinary fistula, and penicillin rash in one patient each.

TABLE 3. Weight of surgical specimens

| Weight        | Cases | Weight                | Cases |
|---------------|-------|-----------------------|-------|
| 10-19 gm..... | 2     | 60-69 gm.....         | 10    |
| 20-29 gm..... | 4     | 70-79 gm.....         | 5     |
| 30-39 gm..... | 12    | 80-89 gm.....         | 7     |
| 40-49 gm..... | 12    | 90-99 gm.....         | 3     |
| 50-59 gm..... | 9     | 100 gm. and over .... | 6     |



FIG. 1. 1, Low power photomicrograph showing typical infarct of prostate. A, hemorrhagic zone of infarct. B, ischemic zone of infarct. C, squamous cell metaplasia. 2, High power photomicrograph. Squamous cell metaplasia. 3, High power photomicrograph. Squamous cell metaplasia on periphery of infarct. 4, High power photomicrograph. A, squamous cell metaplasia. B, corpus amylacea.

## PATHOLOGICAL STUDY

The 6 largest specimens weighed 100, 109, 160, 165, 188, and 386 gm. (table 3). The average weight of all the specimens was 64 gm. This agreed with Baird, McKay, and Kimmelstiel who found the weight in benign prostatic hypertrophy with infarcts twice that without infarcts.

The gross appearance of the infarcted area of the resected prostatic tissue consisted of a rather well circumscribed, roughly ovoid or round zone occurring either singly or multiply and scattered throughout the hyperplastic tissue (fig. 1, 1). The color varied from a bright red to a mottled dull reddish brown or gray. The area was seen frequently protruding slightly from the cut surfaces. In the largest specimen, which weighed 386 gm., these hemorrhagic zones formed conglomerations measuring as much as several centimeters in diameter. The presumptive diagnosis of infarct of the prostate was made by gross examination in 41 (59 per cent) specimens.

The microscopic picture most frequently observed was that of ischemic necrosis, i.e. the infarcted tissue appearing ghost-like with the cell outline and structure only faintly or not at all discernible. Surrounding the lesion was hemorrhage varying in quantity, with some polymorphonuclear and lymphocytic infiltration. Some infarcts had hemorrhage within their confines. On the periphery of the lesion were varying numbers of individual groups of numerous epithelial cells (fig. 1, 2 and 3). These cells had large, pale, bluish-gray cytoplasm and small dark nuclei and occasionally were arranged in clumps or sheets. Within the center of some of these cell groups were pink staining oval structures, having the appearance of corpora amylacea (fig. 1, 4). No keratinization was present. These epithelial cells definitely are not malignant or pre-malignant changes as thought by some in the past.

Moore feels these epithelial cells represent true squamous metaplasia since he saw "on rare occasions true intercellular bridges . . . between the cells." Kimmelstiel could identify neither keratinization nor intercellular bridges.

In the microscopic slides of 46 of the 70 specimens the urethra was well visualized. In 39 (85 per cent) of 46 cases, hyperplasia of a stratified transitional cell type was noted in the urethra and/or the prostatic ducts. Evidence of acute or chronic prostatitis was present in 30 cases (43 per cent). Adenocarcinoma of the prostate was present in 3 cases (4.3 per cent).

## DISCUSSION

The etiology and pathogenesis of the infarct of the prostate and the so-called squamous metaplasia still remain unexplained. Aside from the infarct itself, certain facts are known. According to Abeshouse, periprostatic venous plexus thrombosis in the aged patient is frequently seen. A case of infarct due to multiple emboli from mural thrombi in the left ventricle of the heart has been reported by Hubly and Thompson, but this is obviously a rare finding. The branches of the prostatic arteries supplying the hyperplastic tissue, as described by Flocks, do occupy a vulnerable position near the vesical neck. The tense hyperplastic tissue per se may exert a pressure effect on the vascular supply of the prostate.

The role of instrumental trauma is difficult to exclude. All cases in this series were examined cystoscopically before operation. In addition, a history of other forms of urethral trauma is not uncommon, i.e. preliminary drainage by indwelling or intermittent catheterization, urethral sounding, or prostatic massage. Stewart, Sweetser and Delory reported a case with recent infarcts following catheterization with a metal catheter. High serum acid phosphatase values returned to normal following prostatectomy. Sutton and McDonald noted that 51.9 per cent of their secondary transurethral resections had prostatic infarcts when done 2 to 4 weeks after the first operation. One of the cases in our series had no evidence of infarction in the transurethrally resected prostatic tissue from the first operation. However, there was considerable infarction, with changes in the ductal epithelium, in the specimens obtained 18 days later at the secondary procedure. This study indicates a high incidence of acute urinary retention, gross hematuria, as well as the advanced age and very large mass of hyperplastic tissue in patients with prostatic infarction. Infection apparently has not been present in a high percentage of cases either in the authors' or in other series.

There is a fascinating collection of experimental observations by numerous workers, which is of great interest and might conceivably have a bearing on the pathogenesis of infarcts. Moore mentioned his unpublished work on the canine prostate, using the Carrel-Lindbergh pump. He found metaplasia of the epithelium surrounding an infarct within 3 days in a manner similar to that seen in man. In 1894, Aschoff demonstrated the presence of squamous epithelium in the utriculus masculinus and peri-urethral glands of the newborn child. Schlaeta confirmed this finding and mentioned the appearance of the same entity in the 8 month old fetus and its disappearance after the first 2 months of life. Lacassagne produced epidermoid metaplasia of the prostate in rats with large doses of female sex hormones. Burrows noted similar metaplasia, increased stroma, and polymorphonuclear leukocytic infiltration in animals. Krichesky and Benjamin gave intact rabbits large doses of estrogens to produce atrophy of intra-ocular prostatic implants and found that estrogen administered after castration atrophy had manifested itself, produced marked enlargement of the implants. The atrophy was due to glandular involution, while the enlargement was due to an increase in fibrous and muscle tissue and hyperplasia and metaplasia of the epithelium. Hisaw and Lendrum confirmed the work of others that large doses of estrogens can cause squamous metaplasia of the cervix of the monkey. The lesions regressed after cessation of therapy. Korenchevsky and Dennison found that the addition of small amounts of testicular hormone caused the fibromuscular increase and squamous metaplasia of the prostate, caused by estrone in rats, to return to normal. Estrogenic substance found in the urine of the stallion was not found in the urine of the gelding. Dorfman, Gallagher and Koch found estrogens in the human male urine and in the testis of the bull. Berthrong, Goodwin, and Scott reported squamous metaplasia of the prostate in a dog with an estrogenic secreting Sertoli cell tumor. Lynch and Scott confirmed Teilum's finding of decreased lipid content in the interstitial cell and a corresponding increase in the Sertoli cell in the human testis in advancing age. They did not agree with Teilum's

finding of increased Sertoli cell lipid in benign prostatic hypertrophy. Laqueur and de Jongh mentioned the presence of estrogenic material in the human testis, while recently, Goldzieher reported the isolation of estrogen from the combined extracts of 687 testes. Moore and McLellan studied the effects of sex hormones on the human prostate. No effect was noted with androgens, but estrogens increased the stratification of the usual transitional cell epithelium of the urethra and ducts. Squamous cell metaplasia plus polymorphonuclear leukocytic infiltration between the cells were seen. Ductal changes are sometimes seen in benign prostatic hypertrophy without estrogen therapy where there is not squamous, but transitional change, as shown in the present work. Inglis gave stilbesterol to a case of metastatic carcinoma, thought to be primary in the prostate and extensive squamous metaplasia resulted. A case of true carcinoma of the prostate, treated with large doses of estrogen at Sinai Hospital, had a similar finding. Moore et al. studied the effect of estrogens on smooth muscle. Myomatous nodules from the prostate were sensitive to estrogenic stimulation and smooth muscle from the stomach was not. Emmons and Parkes and Zuckerman posed the possibility of excessive estrogenic substances upsetting an androgen-estrogen balance to produce benign prostatic hypertrophy. This was the basis for the treatment of this condition with androgens for a few years.

From all these data the following questions may be posed. Has estrogenic substance anything to do with infarction? Are the epithelial changes surrounding the infarct the effect of the stimulation of injury to a hormonally sensitive tissue? Do large amounts of hormone over a short period of time reproduce the effects of minute amounts over the span of many years? It is necessary to study further the presence of isolated hyperplastic, dysplastic or metaplastic changes in the glandular epithelium, in the urethral and ductal epithelium, in the fibromuscular tissue of the prostate, as well as the testis and the other endocrine glands and their relation to the prostate.

#### SUMMARY

A study of 70 cases of infarct of the prostate is presented.

The incidence of gross hematuria and acute urinary retention, the age of the patient, and the mass of prostatic tissue were greater in patients with such infarcts.

The role of trauma is questionable in the development of prostatic infarcts: The trauma may be due either a) to pressure of hyperplastic tissue, b) instrumental trauma before operation, c) effect of electrocoagulation or fulguration.

The etiology and pathogenesis of prostatic infarction and concomitant epithelial changes are discussed.

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## IMPLANTATION OF CANCER OF THE PROSTATE IN SITE OF PERINEAL NEEDLE BIOPSY: REPORT OF A CASE

B. G. CLARKE, WYLAND F. LEADBETTER AND JAMES S. CAMPBELL

*From the Departments of Urology and Pathology, Tufts College Medical  
School and the New England Medical Center, Boston, Mass.*

We present the history of a patient in whom local implantation of cancer occurred in the perineal subcutaneous tissue traversed by a biopsy needle. This is the first such case of which we have been able to find record. That such a complication may occur makes caution necessary in the selection of patients for this diagnostic procedure.

Pearson and Nickerson, in their report of 36 cases of perineal biopsy with the Silverman needle, made no mention of local implantation of cancer as a sequel. Rinker and Shurman, who performed 152 biopsies with the Turkel needle, recorded no instance of such implantation and stated that they knew of no one who had observed this. Veenema did not mention the complication in his description of a new perineal biopsy instrument.

Biologic evidence from other sources indicates that manipulative implantation of prostatic cancer is possible. In a group of 115 personally observed cases of prostatic cancer submitted to total prostatovesiculectomy we have one patient in whom simultaneous cystectomy was performed because the lesion had extended to surround the intramural ureters. In this patient extensive cancerous implantation developed in his abdominal operative wound. Deming and Hovenian have successfully transplanted human prostatic cancer into the anterior chamber of the guinea pig's eye.

### CASE REPORT

A 70 year old man (H. A., No. 65053) came under our observation in January 1952, ten months after transurethral resection for prostatic obstruction. During the interval he had been maintained on stilbestrol, but mild obstructive symptoms recurred. Examination disclosed a fixed stony hard prostate, not strikingly enlarged but with evident extension about the seminal vesicles. There was no evidence of pulmonary, skeletal or lymphatic metastasis, and the serum acid phosphatase was not elevated. A specimen of prostatic tissue, histologic study of which showed cancer (fig. 1), was obtained with the Moonen perineal biopsy needle, and castration was performed. Stilbestrol 5 mg. were prescribed daily. The symptoms of prostatic obstruction improved. Within 10 months, obstructive symptoms recurred and a second transurethral resection was performed which yielded tissue similar in histologic appearance to that previously obtained by needle biopsy (fig. 2). Because some portions of this specimen showed squamoid metaplasia, a tumor dose of 3700 units was delivered to the prostatic area by external radiation. Under this treatment slight diminution in the size of the tumor occurred. Stilbestrol was continued.



FIG. 1. Specimen of prostatic adenocarcinoma obtained by perineal needle biopsy after 10 month period of maintenance on stilbestrol.



FIG. 2. Tissue obtained at transurethral resection 9 months following perineal needle biopsy and castration. In some areas, carcinoma showed inconspicuous squamoid metaplasia.

In February 1953, thirteen months after perineal needle biopsy, the patient remained symptomatically well but a small hard nodule 3 mm. in diameter was identified in the subcutaneous tissue of the perineum which had been traversed

by the perineal needle puncture. This was not fixed to the skin or to deeper fascial structures. There was no evidence of metastasis elsewhere. Palpation of the prostate disclosed no appreciable change since the previous examinations, and

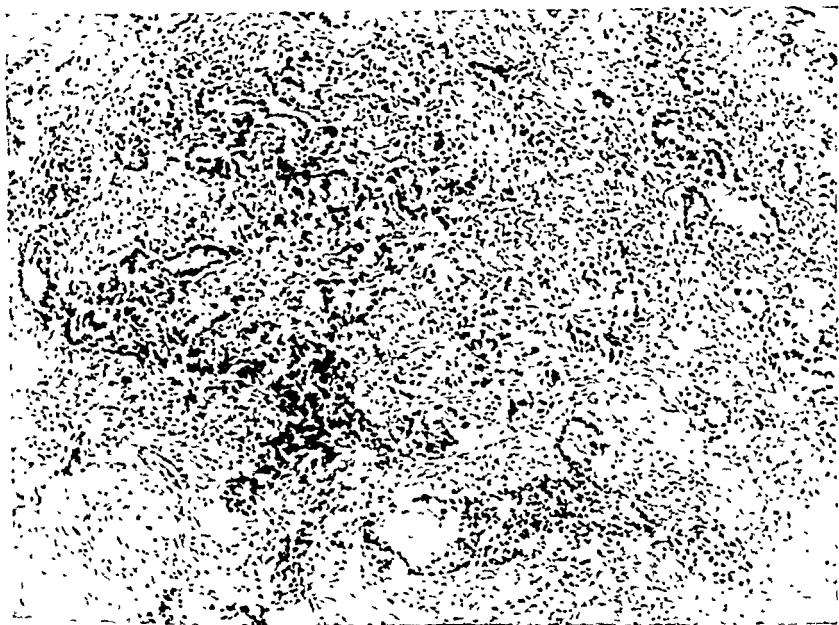


FIG. 3. Nodule of implanted cancer excised from perineal subcutaneous tissue 13 months after needle biopsy and castration, and following 23 months of maintenance on stilbestrol

the patient's general condition remained good. The subcutaneous nodule was locally excised and histologic examination (fig. 3) showed cancer similar in structure to that previously identified by needle biopsy and transurethral resection. The site of excision healed well with no residual local induration.

#### SUMMARY

A case is reported in which prostatic cancer was transplanted to the subcutaneous tissues of the perineum as a result of perineal needle biopsy. Caution is necessary in the selection of patients for this diagnostic procedure.

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## OSTEITIS PUBIS TREATED WITH CORTISONE

JAMES J. NUGENT

Osteitis pubis is an extremely painful disease for which there has been no satisfactory treatment. The effect of the administration of cortisone to one patient who had osteitis pubis is presented in this paper in order that others may attempt to relieve patients of the extreme pain while data are being accumulated to evaluate the use of cortisone. The following case history is presented:

On March 19, 1951, a suprapubic prostatectomy was done on Mr. W. R. aged 65. The pathologist made a report of benign hypertrophy of the prostate and chronic prostatitis. The surgeon considered the postoperative course to be normal and the patient was dismissed from the hospital on the fourteenth day. Convalescence continued uneventful and the patient felt fine until the sixth week when he began to have pain in the pubic area. The onset was gradual and the severity of the pain became steadily greater until, when the patient presented himself to me on June 28, he was hardly able to walk. He had arranged some ropes on his bed to assist him in getting out of bed and, because of this difficulty, he spent most of his time sitting in a chair. He thought that his pain was arising in his scrotum or his penis and radiating down the medial sides of his thighs. His urinary stream, since the operation, had been excellent and he was happy about the operation except for the pain. His past history was not pertinent to the present illness. He was not having fever or urinary symptoms.

After watching the patient walk from the waiting room to the consultation room and listening to his story, the proper diagnosis was suspected. Physical examination was normal except for the following:

In the abdomen, no organs or masses were palpable and there was no tenderness. There was a well healed suprapubic scar. Pressure over the symphysis pubis caused pain, grade 4 (on the basis of 1 to 4). There was no induration or discoloration. The left epididymis was indurated, grade 2, and enlarged, grade 1. There was a hydrocele on the left estimated to contain about two ounces of fluid. There was no tenderness to palpation of the scrotal contents, penis or perineum. The prostate was normal size, smooth, resilient, fixed grade 1 and not tender. Any movement of the patient's legs, either active or passive, caused severe pain in the pelvis with spasm of the adductor muscles of the thigh. The feet could not be separated more than twelve inches.

Urinalysis was normal. A scout film of the abdomen showed the symphysis pubis to be 11 mm. in width. There was irregularity in the density and contour of the bone of the joint. There was marked osteo-arthritis of the spine. There was no evidence of urinary or prostatic calculi.

Proceeding on the principle that osteitis pubis is a low-grade infection, according to the report of Lavalley and Hamm,<sup>1</sup> the patient was given 300,000 units of

Accepted for publication December 8, 1952.

<sup>1</sup> Lavalley, L. L. and Hamm, F. C.: *J. Urol.*, 66: 418, 1951.

penicillin and 1 gm. dihydrostreptomycin in the office. He received 12 gm. of terramycin in the next 48 hours. He was given codeine and told to take as much as necessary to relieve his pain.

Two or three times a week, the patient called to state that he was no better. On July 12, he was given  $\frac{1}{6}$  gr. morphine tablets and advised to use them freely. Since the syndrome had been present for a little over two months, it was hoped that it was about to run its course and that relief might occur spontaneously. However, the patient considered that his pain was getting worse, if possible.

Although the patient could ill afford it, it was decided to administer cortisone for whatever benefit might be derived. At 4 p.m. on July 19, 50 mg. of cortisone was administered by mouth without noticeable effect. The second dose of 50 mg. was administered at 8 p.m. after which time the patient fell asleep. When he was awakened by his wife at midnight to take the third dose of 50 mg., he recognized that he had about 80 per cent relief of his discomfort. The dosage of 50 mg. every 4 hours was continued for the first 24 hours. The patient was able to move around and walk with little discomfort. In this respect, cortisone was much more beneficial than narcotics which gave some relief when the patient was quiet but gave little relief when he moved.

In the interest of economy, the dosage was reduced to 25 mg. every 4 hours. At the end of 3 days, the patient reported that the 300 mg. of cortisone administered in the first 24 hours had given him about 80 per cent relief of pain while 300 mg. of cortisone in the following 48 hours had given him almost no relief of pain. The dosage was then increased to 50 mg. every 4 hours and again he felt that he was relieved of 80 per cent of his pain.

In trying to reduce the expense, the patient varied the frequency and the amount of the drug during the next seventeen days, a total of 2,600 mg. being administered during this period. He found that three or four successive doses of 50 mg. of cortisone gave him about 80 per cent relief of his pain. Any amounts less than this resulted in a return of the pain and, at the end of 17 days, he considered that he had about 80 per cent as much pain as when the drug was first started. At the end of 4 weeks, he had taken 4,600 mg. of cortisone without ill effect. He restricted his sodium chloride intake and had supplementary potassium chloride. No other precautions were taken.

He continued with smaller doses of cortisone, taken less frequently, and was able to keep himself quite comfortable by the use of aspirin which seemed to give him more relief than codeine or morphine.

During the month of September 1951, the patient presented himself to a radiologist who administered eight x-ray treatments to the symphysis. He was not aware of any immediate change in his symptoms. He continued to take gradually decreasing doses of cortisone until the last week of November 1951. Gradually, his pain diminished and he had no pain after about Christmas 1951. On the second of February 1952, an x-ray showed that the symphysis was almost exactly the same as it was shown on the x-ray in July 1951. The patient was without complaints and had resumed all of his previous activities.

## COMMENT

The relief of pain was satisfactory and the patient states that it was worth the money which he could ill afford to spend. Cortisone did not apparently change the course of the disease. It did, however, give the patient considerable relief of his pain while it was being administered. These observations seem to be about the same as those reported by Whitmore, et al.<sup>2</sup> who used ACTH in 3 cases of osteitis pubis. It is hoped that other observers will report their results in order that the true value of cortisone in osteitis pubis may be obtained.

## SUMMARY

A case of osteitis pubis treated with cortisone is presented. Cortisone, in adequate dosage, gave considerable relief of pain. Cortisone, in inadequate dosage, gave almost no relief of pain. Cortisone did not apparently change the course of the disease in this case.

*1714 Biscayne Blvd., Miami 32, Fla.*

<sup>2</sup> Whitmore, W. F., Marshall, V. F., Poppell, J. W., Grant, R. N., Petro, A. T. and Rawson, R. W.. Osteitis Pubis Treated With Adrenocorticotrophic Hormone. *Proceedings of the second Clinical ACTH Conference*, vol. 2, Therapeutics. Philadelphia: Blakiston Co., 1951.

## MYXOFIBRO-ANGIOMA OF CORPUS SPONGIOSUM

H. SPENCER HOYT

*From the Department of Surgery, Division of Urology, Stanford University School of Medicine, San Francisco, Calif.*

Carcinoma arising from the epithelium of the glans is by far the most common tumor of the penis. Mesothelial tumors, however, do occur and have been the subject of increasing interest, particularly during the past decade (table 1). Attention was called to the mesothelial group in 1924 by Joelson, who at that time was able to find reports of 35 cases. He classed them as 1) fibrosarcomas of the spindle cell and mixed cell type, 2) round cell sarcomas, 3) melanosarcomas, and 4) endotheliomas.

Foulds and Flett presented an excellent review in 1938 and reported a case of malignant endothelioma of the corpora cavernosa.

In 1944 Wattenburg reviewed particularly the malignant tumors and found 8 cases of fibrosarcoma, 10 cases of melanosarcoma, and 7 cases of malignant endothelioma.

Confining their report to the endothelioma of the penis, Coppridge, Putnam and Miale in 1946 were able to find 12 cases, including both benign and malignant types.

The latest report, that of Mortensen and Murphy in 1950, is confined to the benign vascular lesions of the glans only. They were able to find 8 cases in the literature and added two of their own, bringing the total number of reported cases to 10.

Involvement of the body or shaft of the penis with tumors originating from the vascular endothelium is even more rare. Apparently only 2 cases have been reported. Rabson, and Balog and Cerqua have each reported 1 case of pea-sized tumor arising from the corpora cavernosa deep in the perineum.\*

This report details the third benign endothelioma of the shaft of the penis to be reported, and the first case of a sizeable pedunculated tumor.†

### CASE REPORT

M. C., aged 51, requested examination of a lump on the side of the penis. It had been present for 7 years, and followed a bump. It had slowly increased in size until the last 6 months, when it had grown more rapidly. There had been no pain or subjective symptoms other than a sense of weight. Family history and past history were noncontributory.

Physical examination showed a smooth, pedunculated tumor arising from the middle of the shaft on the right side, being of firm consistency and loosely attached to the deeper tissues (fig. 1).

\* Involvement of both corpora with endothelioma has been reported in two instances, one case by Yamamoto and a second case by Alexander and Dunham. These 2 cases have been classified as malignant in Wattenburg's report.

† Since finishing the above report a further case of malignant epithelioma has been reported by W. D. Cornwall and L. Whitaker in the *Journal of Urology* (vol. 69, p. 307-8, 1953).



TABLE 1. *Endothelioma of penis: Summary of reported cases*

| MALIGNANT            |                                   | BENIGN                    |                                                                        |                  |
|----------------------|-----------------------------------|---------------------------|------------------------------------------------------------------------|------------------|
| Wattenberg, 1944     | Coppridge, Putnam and Miale, 1946 | Glans                     | Urethra                                                                | Corpora          |
| Maurer               | Maurer                            | Mortensen and Murphy 1950 | Hauser*                                                                | Rabson           |
| Alexander and Dunham | Alexander and Dunham              | Kroll                     | Kroll†                                                                 | Balog and Cerqua |
| Hildebrand           | Hildebrand                        | Seiffert                  |                                                                        | Hoyt             |
| Colmers              | Colmers                           | Pawlowski                 |                                                                        |                  |
| Yamamoto             | Creite                            | Seligman                  |                                                                        |                  |
| Balog and Cerqua     | Pelagatti                         | Gibson                    |                                                                        |                  |
| Foulds and Flett     | Gobbi                             | Pearlman                  | * Cited by Kroll, hemangioma in posterior urethra of 17-day old infant |                  |
|                      | Yamamoto                          | Gorodner                  |                                                                        |                  |
|                      | Balog and Cerqua                  | Dubreuil-Chambardel       | † Involved both glans and urethra                                      |                  |
|                      | Foulds and Flett                  | Mortensen and Murphy      |                                                                        |                  |
|                      | Coppridge et al.                  |                           |                                                                        |                  |



FIG. 1. Tumor arising from shaft of penis (Patient insisted on keeping scrotum and both testes beneath the clothing)



FIG. 2 Gross appearance of inside of tumor

Operation, July 20, 1945: The tumor was removed under pentothal anesthesia. It was found grossly attached to the fascia of the shaft and was easily dissected off intact. The wound was closed without drainage.

Pathological report: The gross specimen consisted of a cyst-like structure measuring 7.5 by 6 by 5 cm. with a wall 5 mm. in thickness and the wall at the base of this pedicle is 1 cm. in thickness. The mass appears to be well circumscribed. The center is composed of a serosanguinous fluid. The cyst wall is smooth and contains no papillary projections (fig. 2).



FIG. 3. A, appearance of tumor under low power. B, high power

Microscopic examination showed a well circumscribed capsule in which were young mesenchymal cells which ran all the way from myxomatous to fibroblastic proliferation. There was also a tendency to form some endothelial channels and there were occasionally very large venous sinusoids. Mitoses were found, but these were not too numerous (fig. 3). Diagnosis: Myxofibroangioma (probably derived from corpus spongiosum). Jesse L. Carr, M.D.

There has been no evidence of recurrence to date, 5½ years postoperatively.

#### SUMMARY

Twelve cases of benign endothelioma of the penis previously have been reported. Ten of these involved the glans and the others were small pea-sized growths arising from the corpora cavernosa. A third case of endothelioma arising from the corpus spongiosum is recorded. It is apparently the first case to be reported describing a large tumor.

409 Professional Bldg., Monterey, Calif.

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## THE EFFECT OF ANTIBIOTICS ON SPERMATOZOA IN VITRO, SPERMATOGENESIS AND THEIR CONCENTRATION IN TESTICULAR TISSUES

HARRY SENECA AND DIANE IDES

*From the Department of Urology and Microbiology, College of Physicians and Surgeons,  
Columbia University, New York, N. Y.*

According to Easterbrook<sup>1</sup> the best preservative for bull semen is 500 mcg. dihydrostreptomycin and 0.5 per cent sulfanilamide in egg yolk and 2.9 per cent buffered sodium citrate.

Carminati<sup>2</sup> reported that Chloromycetin inhibited human spermatozoa in 0.5 to 2.0 mg. per ml. in the first few minutes and Tyrothrycin in 66.6 mcg. per ml. inhibited the spermatozoa in ten minutes.

The authors<sup>3</sup> previously reported on the in vitro effect of antibiotics on human spermatozoa. Polymyxin had stimulating effect. Isonicotinic acid hydrazide was non-toxic. Penicillin, streptomycin, Terramycin, Aureomycin, and neomycin were slightly toxic. Magnamycin and Viomycin were mildly toxic, while bacitracin, fumagillin, Rimocidin and Thiolutin were moderately toxic.

The present studies were undertaken to determine:

- 1) The survival rate of spermatozoa in various concentrations of antibiotics,
- 2) The effect of antibiotics on spermatogenesis, and
- 3) The concentrations of antibiotics in testicular tissue.

### MATERIAL AND METHODS

The spermatozoa were collected directly into sterile Petri dishes from young healthy adults. The count varied from 100,000,000 to 120,000,000 spermatozoa per ml. The water soluble antibiotics and isonicotinic acid hydrazide were dissolved serially in sterile saline. The non-water soluble antibiotics, Thiolutin, Rimocidin and fumagillin were dissolved in 70 per cent ethyl alcohol and then serially diluted in sterile saline. One-half ml. of the diluted antibiotic was put in sterile Kahn test tube and then one-half ml. of semen containing actively motile spermatozoa was added. The entire procedure was carried out under sterile conditions. The tubes were then kept at room temperature and at various intervals of time up to 51 hours 40 minutes a loopful of the contents of the tubes was examined under the low and high power of the microscope for motility as well as structural changes in the spermatozoa.

Six to eight week old male white rats were used in these experiments. The weight varied from 80 to 110 gm., the average was 100 gm. The following antibiotics were included in these studies: potassium penicillin G, Terramycin

This work was supported by a Grant from Charles Pfizer & Company, Brooklyn, N. Y. In vitro observations (read at the annual meeting, A. U. A. St. Louis Mo. May 12, 1953.)  
<sup>1</sup> Easterbrook, H. L.: Antibiotic treatment of diluted bull semen used in artificial insemination. *Fertility and Sterility* 2: 430-443, 1951.

<sup>2</sup> Carminati, G. M.: *Boll. D. Ist. seroterap. milanese* 30: 550-556, 1951.

<sup>3</sup> Seneca, H. and Ides, D.: Effect of antibiotics on human spermatozoa. *J. Urol.* 70: 306-311, 1953.

intramuscular 4A (Terramycin plus 2 per cent procaine hydrochloride), streptomycin sulfate, Magnamycin chloride, bacitracin (parenteral), and polymyxin (parenteral). The antibiotics were injected intramuscularly five times a week for 6 weeks. During the course of the experiments, at intervals of 24 hours, 2 weeks, 4 weeks and 6 weeks, the rats were killed with ether, the testes were removed under sterile technique, one was preserved for microscopic examination and the second testis was assayed to determine the concentrations of the antibiotics per gram of testicular tissue. In the first determination, rats were sacrificed and the testes were removed 15 hours after the injection of the single dose of the antibiotic. In the second (2 weeks), third (4 weeks), and fourth (6 weeks) determinations, the rats were sacrificed and the testes were removed 16 hours after the last dose of the antibiotic.

Potassium penicillin G was injected intramuscularly in 100,000 units. The first determination was after a single dose of 100,000 units. The second determination was done after two weeks of treatment which included 10 injections of 100,000 units. The control animal weighed 137 gm., the penicillin rat 140 gm. The third determination was done after 4 weeks of treatment with 20 injections of 100,000 units. The control rat weighed 250 gm., the penicillin rat 200 gm. The fourth determination was done after 6 weeks of treatment which included 30 injections of 100,000 units. Both the control rat and penicillin rat weighed 250 gm.

Terramycin intramuscular 4A (Terramycin plus 2 per cent procaine hydrochloride) was injected intramuscularly in 11 mg. doses. The first determination was following the injection of a single dose. The second determination was made after 2 weeks of treatment with 10 injections of 11 mg. The control rat weighed 137 gm., the Terramycin rat 190 gm., a net gain of 53 gm. The third determination was after four weeks of treatment with 20 injections of 11 mg. The control and Terramycin rats weighed 200 gm. The fourth determination was made after 6 weeks of Terramycin treatment with 30 injections of 11 mg. The control and Terramycin rats weighed 250 gm.

Streptomycin sulfate was injected intramuscularly in 10 mg. doses. The first determination was after one dose of 10 mg. The second determination was done after 2 weeks of streptomycin treatment with 10 injections of 10 mg. intramuscularly. The control rat weighed 137 gm., while the streptomycin rat weighed 150 gm., a net gain of 13 gm. The third determination included 4 weeks treatment with 20 injections. The control rat weighed 200 gm., while the streptomycin rat weighed 235 gm., a net gain of 35 gm. The fourth determination was after 6 weeks treatment with 30 injections of 10 mg. The control rat weighed 250 gm., but the streptomycin rat weighed 240 gm.

Magnamycin hydrochloride was injected intramuscularly in 10 mg. doses. The first determination was made after a single injection of 10 mg. The second determination was after 2 weeks of Magnamycin injection, with 10 injections of 10 mg. The control rat weighed 137 gm., the Magnamycin rat 150 gm., a gain of 13 gm. The third determination was made after 4 weeks of Magnamycin injection with 20 injections of 10 mg. The control rat weighed 200 gm., while

the Magnamycin rat weighed 170 gm., a loss of 30 gm. The fourth determination was done after 6 weeks of Magnamycin treatment with 30 injections of 10 mg. The control rat weighed 250 gm., the Magnamycin rat 200 gm., a net loss of 50 gm.

Bacitracin (parenteral) 50,000 units, was injected intramuscularly in 1,000 unit doses. The first determination was done following the single injection of 1,000 units of bacitracin intramuscularly. The second determination was after 2 weeks of bacitracin treatment with 10 injections of 1,000 units intramuscularly. The control rat weighed 137 gm., bacitracin rat 95 gm., a net loss of 42 gm. The third determination was done after 13 injections of 1,000 units bacitracin intramuscularly. None of these rats tolerated more than 13 injections of bacitracin. The rat was sacrificed 9 days after the thirteenth dose. The control rat weighed 200 gm., the bacitracin rat weighed 148 gm., a net loss of 52 gm. No further determination was available on these rats.

Polymyxin (parenteral 500,000 units) was injected intramuscularly. The first determination was done after a single injection of 500 units of polymyxin. The second determination was after 2 weeks of injection with 7 doses of 500 units and 3 doses of 1,000 units, total 6,500 units. The control rat weighed 137 gm., the polymyxin rat 180 gm., a net gain of 43 gm. The third determination was done after 4 weeks of polymyxin injection with 20 injections including 3 doses of 1,000 units and 17 doses of 500 units, total 11,500 units. The control rat weighed 200 gm., the polymyxin rat 230 gm., a net gain of 30 gm. The fourth determination was following 6 weeks of treatment with 30 injections of polymyxin with 3 doses of 1,000 units and 27 doses of 500 units, total 16,500 units. The control rat weighed 250 gm., while the polymyxin rat weighed 200 gm.

## RESULTS

Table 1 shows in a tabular form the *in vitro* effect of antibiotics on human spermatozoa. Penicillin in a concentration of 500 units per ml. completely immobilized the spermatozoa in 47 hours 45 minutes, while in concentrations varying from 2,500 to 0.75 units per ml., about 5 per cent of the spermatozoa were still motile. Streptomycin in 2,500 to 19.53 mcg./ml. immobilized the spermatozoa in 39 hours 15 minutes, and in 9.76 mcg./ml. some were motile in 47 hours 45 minutes. Bacitracin in a concentration of 1,250 units per ml. showed a progressive diminution in the motility of the spermatozoa. In 1 hour approximately 75 per cent were non-motile, in one and a half hours 95 per cent were non-motile, and in 2 hours there was lysis which at first was moderate, but it became complete in 2 hours 40 minutes. In 125 units per ml. even though there were more motile spermatozoa in 1 hour and 1½ hours, yet lysis was complete in 2 hours 40 minutes. In a concentration of 0.125 units per ml. the spermatozoa showed very little change in the first 4 hours but thereafter there was a gradual loss in the motility so that in 24 hours there were very few motile spermatozoa, and within 49 hours 40 minutes all were completely immobilized. In a concentration of 0.3125 to 0.0625 units per ml., at the end of 49 hours 40 minutes there were still a few motile spermatozoa. Polymyxin in concentra-

TABLE 1

|         |          | PENICILLIN   |     |         |          |          |          |          |          |         |         |         |         |
|---------|----------|--------------|-----|---------|----------|----------|----------|----------|----------|---------|---------|---------|---------|
|         |          | 7'           | 75' | 2½ hrs. | 15½ hrs. | 22½ hrs. | 24½ hrs. | 39½ hrs. | 47½ hrs. |         |         |         |         |
| 5,000   | units/ml | +            | +   | +       | +        | +        | +        | +        | —        |         |         |         |         |
| 2,500   | units/ml | +            | +   | +       | +        | +        | +        | +        | +        |         |         |         |         |
| 1,250   | units/ml | +            | +   | +       | +        | +        | +        | +        | +        |         |         |         |         |
| 625     | units/ml | +            | +   | +       | +        | +        | +        | +        | +        |         |         |         |         |
| 312.5   | units/ml | +            | +   | +       | +        | +        | +        | +        | +        |         |         |         |         |
| 156.25  | units/ml | +            | +   | +       | +        | +        | +        | +        | +        |         |         |         |         |
| 78      | units/ml | +            | +   | +       | +        | +        | +        | +        | +        |         |         |         |         |
|         |          | STREPTOMYCIN |     |         |          |          |          |          |          |         |         |         |         |
|         |          | 7'           | 75' | 2½ hrs. | 15½ hrs. | 22½ hrs. | 24½ hrs. | 39½ hrs. | 47½ hrs. |         |         |         |         |
| 2,500   | mcg/ml   | +            | +   | +       | +        | +        | +        | +        | —        |         |         |         |         |
| 1,250   | mcg/ml   | +            | +   | +       | +        | +        | +        | —        | —        |         |         |         |         |
| 625     | mcg/ml   | +            | +   | +       | +        | +        | +        | —        | —        |         |         |         |         |
| 156.25  | mcg/ml   | +            | +   | +       | +        | +        | +        | —        | —        |         |         |         |         |
| 78.125  | mcg/ml   | +            | +   | +       | +        | +        | +        | —        | —        |         |         |         |         |
| 39.06   | mcg/ml   | +            | +   | +       | +        | +        | +        | —        | —        |         |         |         |         |
| 19.53   | mcg/ml   | +            | +   | +       | +        | +        | +        | —        | —        |         |         |         |         |
| 9.76    | mcg/ml   | +            | +   | +       | +        | +        | +        | +        | +        |         |         |         |         |
|         |          | BACITRACIN   |     |         |          |          |          |          |          |         |         |         |         |
|         |          | 5'           | 30' | 60'     | 90'      | 2 hrs    | 2½ hrs   | 3½ hrs   | 4 hrs    | 17½ hrs | 21½ hrs | 25½ hrs | 49½ hrs |
| 1,250   | units/ml | +            | +   | +       | +        | Lysis    | —        | —        | —        | —       | —       | —       | —       |
| 125     | units/ml | +            | +   | +       | +        | Lysis    | —        | —        | —        | —       | —       | —       | —       |
| 12.5    | units/ml | +            | +   | +       | +        | +        | +        | +        | +        | —       | —       | —       | —       |
| 1.25    | units/ml | +            | +   | +       | +        | +        | +        | +        | +        | —       | —       | —       | —       |
| 0.125   | units/ml | +            | +   | +       | +        | +        | +        | +        | +        | +       | +       | +       | —       |
| 0.0625  | units/ml | +            | +   | +       | +        | +        | +        | +        | +        | +       | +       | +       | +       |
| 0.03125 | units/ml | +            | +   | +       | +        | +        | +        | +        | +        | +       | +       | +       | +       |
|         |          | POLYMYXIN    |     |         |          |          |          |          |          |         |         |         |         |
|         |          | 10'          | 70' | 2 hrs   | 3 hrs    | 19½ hrs  | 25½ hrs  | 29½ hrs  | 51½ hrs  |         |         |         |         |
| 10,000  | units/ml | +            | +   | +       | +        | +        | +        | +        | +        | +       | +       | +       | +       |
| 1,000   | units/ml | +            | +   | +       | +        | +        | +        | +        | +        | +       | +       | +       | +       |
| 100     | units/ml | +            | +   | +       | +        | +        | +        | +        | +        | +       | +       | +       | +       |
| 10      | units/ml | +            | +   | +       | +        | +        | +        | +        | +        | +       | +       | +       | +       |
| 1       | units/ml | +            | +   | +       | +        | +        | +        | +        | +        | +       | +       | +       | +       |
| 0.1     | units/ml | +            | +   | +       | +        | +        | +        | +        | +        | +       | +       | +       | +       |
| 0.01    | units/ml | +            | +   | +       | +        | +        | +        | +        | +        | +       | +       | +       | +       |
|         |          | TERRAMYCIN   |     |         |          |          |          |          |          |         |         |         |         |
|         |          | 7'           | 75' | 2½ hrs  | 4 hrs.   | 14½ hrs. | 22½ hrs  | 39½ hrs. | 47½ hrs. |         |         |         |         |
| 12.5    | mg/ml    | —            | —   | —       | —        | —        | —        | —        | —        |         |         |         |         |
| 1.25    | mg/ml    | +            | +   | +       | +        | —        | +        | +        | +        |         |         |         |         |
| 125     | mcg/ml   | +            | +   | +       | +        | +        | +        | +        | +        |         |         |         |         |
| 12.5    | mcg/ml   | +            | +   | +       | +        | +        | +        | +        | +        |         |         |         |         |
| 6.25    | mcg/ml   | +            | +   | +       | +        | +        | +        | +        | +        |         |         |         |         |
| 3.125   | mcg/ml   | +            | +   | +       | +        | +        | +        | +        | +        |         |         |         |         |
| 1.56    | mcg/ml   | +            | +   | +       | +        | +        | +        | +        | +        |         |         |         |         |
| 0.78    | mcg/ml   | +            | +   | +       | +        | +        | +        | +        | +        |         |         |         |         |

TABLE 1—Continued

|        |        | AUREOMYCIN   |     |     |     |      |        |       |         |         |         |         |         |         |         |
|--------|--------|--------------|-----|-----|-----|------|--------|-------|---------|---------|---------|---------|---------|---------|---------|
|        |        | 0'           | 18' | 20' | 57' | 70'  | 2 hrs  | 3 hrs | 17½ hrs | 21½ hrs | 25½ hrs | 49½ hrs |         |         |         |
| 12 5   | mg/ml  | +            | +   | +   | +   | —    | —      | —     | —       | —       | —       | —       |         |         |         |
| 1 25   | mg/ml  | +            | +   | +   | +   | +    | +      | +     | —       | —       | —       | —       |         |         |         |
| 125    | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | —       | —       |         |         |         |
| 12 5   | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       |         |         |         |
| 6 25   | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       |         |         |         |
| 3 125  | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       |         |         |         |
| 1 56   | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       |         |         |         |
| 0 78   | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       |         |         |         |
|        |        | VIOMYCIN     |     |     |     |      |        |       |         |         |         |         |         |         |         |
|        |        | 0'           | 7'  | 22' | 44' | 60'  | 77'    | 2 hrs | 3 hrs   | 3½ hrs  | 18½ hrs | 21½ hrs | 24½ hrs | 27½ hrs |         |
| 25     | mg/ml  | +            | +   | +   | +   | +    | +      | —     | —       | —       | —       | —       | —       | —       |         |
| 2 5    | mg/ml  | +            | +   | +   | +   | +    | +      | +     | —       | —       | —       | —       | —       | —       |         |
| 250    | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | —       | —       | —       | —       | —       |         |
| 25     | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       | +       | —       |         |
| 2 5    | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       | +       | +       |         |
| 0 25   | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       | +       | +       |         |
|        |        | NEOMYCIN     |     |     |     |      |        |       |         |         |         |         |         |         |         |
|        |        | 0'           | 9'  | 33' | 60' | 120' | 2½ hrs | 3 hrs | 3½ hrs  | 18½ hrs | 21½ hrs | 24½ hrs | 27½ hrs |         |         |
| 6 25   | mg/ml  | +            | +   | +   | +   | +    | +      | +     | +       | —       | —       | —       | —       | —       |         |
| 0 625  | mg/ml  | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | —       | —       | —       |         |
| 62 5   | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       | +       | +       |         |
| 6 25   | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       | +       | +       |         |
| 0 625  | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       | +       | +       |         |
|        |        | FUSIDIC ACID |     |     |     |      |        |       |         |         |         |         |         |         |         |
|        |        | 0'           | 30' | 60' | 90' | 120' | 160'   | 3 hrs | 18½ hrs | 21½ hrs | 24½ hrs | 27½ hrs |         |         |         |
| 1,250  | mcg/ml | —            | —   | —   | —   | —    | —      | —     | —       | —       | —       | —       | —       | —       |         |
| 125    | mcg/ml | +            | +   | +   | +   | +    | +      | —     | —       | —       | —       | —       | —       | —       |         |
| 12 5   | mcg/ml | +            | +   | +   | +   | +    | +      | +     | —       | —       | —       | —       | —       | —       |         |
| 1 25   | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | —       | —       | —       | —       |         |
| 0 125  | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       | —       | —       |         |
| 0 0125 | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       | +       | —       |         |
|        |        | MAGNAMYCIN   |     |     |     |      |        |       |         |         |         |         |         |         |         |
|        |        | 0'           | 5'  | 20  | 45  | 60   | 76     | 95    | 2 hrs   | 2½ hrs  | 3 hrs   | 3½ hrs  | 19½ hrs | 23½ hrs | 27½ hrs |
| 10     | mg/ml  | +            | +   | +   | —   | —    | —      | —     | —       | —       | —       | —       | —       | —       | —       |
| 1      | mg/ml  | +            | +   | +   | +   | +    | —      | —     | —       | —       | —       | —       | —       | —       | —       |
| 100    | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | —       | —       | —       | —       | —       |
| 10     | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | —       | —       | —       | —       |
| 1      | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       | +       | +       | —       |
| 0 5    | mcg/ml | +            | +   | +   | +   | +    | +      | +     | +       | +       | +       | +       | +       | +       | —       |



TABLE 1—*Concluded*

|        |        | RIMOCIDIN |     |     |     |      |       |        |       |         |         |         |         |
|--------|--------|-----------|-----|-----|-----|------|-------|--------|-------|---------|---------|---------|---------|
|        |        | 0'        | 20' | 30' | 60' | 101' | 2 hrs | 2½ hrs | 3 hrs | 18½ hrs | 21½ hrs | 24½ hrs | 27½ hrs |
| 1,250  | mcg/ml | +         | —   | —   | —   | —    | —     | —      | —     | —       | —       | —       | —       |
| 125    | mcg/ml | +         | +   | +   | +   | +    | +     | +      | —     | —       | —       | —       | —       |
| 12 5   | mcg/ml | +         | +   | +   | +   | +    | +     | +      | +     | +       | —       | —       | —       |
| 1 25   | mcg/ml | +         | +   | +   | +   | +    | +     | +      | +     | +       | +       | —       | —       |
| 0 125  | mcg/ml | +         | +   | +   | +   | +    | +     | +      | +     | +       | +       | +       | —       |
| 0 0125 | mcg/ml | +         | +   | +   | +   | +    | +     | +      | +     | +       | +       | +       | +       |

|        |        | THIOLUTIN |     |     |     |      |      |       |         |         |         |        |
|--------|--------|-----------|-----|-----|-----|------|------|-------|---------|---------|---------|--------|
|        |        | 0'        | 30' | 60' | 90' | 120' | 150' | 3 hrs | 18½ hrs | 21½ hrs | 24½ hrs | 27½ hr |
| 1,250  | mcg/ml | —         | —   | —   | —   | —    | —    | —     | —       | —       | —       | —      |
| 125    | mcg/ml | +         | +   | +   | +   | +    | +    | —     | —       | —       | —       | —      |
| 12 5   | mcg/ml | +         | +   | +   | +   | +    | +    | +     | —       | —       | —       | —      |
| 1 25   | mcg/ml | +         | +   | +   | +   | +    | +    | +     | —       | —       | —       | —      |
| 0 125  | mcg/ml | +         | +   | +   | +   | +    | +    | +     | +       | —       | —       | —      |
| 0 0125 | mcg/ml | +         | +   | +   | +   | +    | +    | +     | +       | —       | —       | —      |

|     |        | ISONICOTINIC ACID HYDRAZIDE |     |     |       |         |         |         |
|-----|--------|-----------------------------|-----|-----|-------|---------|---------|---------|
|     |        | 7'                          | 50' | 120 | 3 hrs | 18½ hrs | 21½ hrs | 27½ hrs |
| 10  | mg/ml  | +                           | +   | +   | —     | —       | —       | —       |
| 1   | mg/ml  | +                           | +   | +   | +     | +       | —       | —       |
| 100 | mcg/ml | +                           | +   | +   | +     | +       | +       | +       |
| 10  | mcg/ml | +                           | +   | +   | +     | +       | +       | +       |
| 1   | mcg/ml | +                           | +   | +   | +     | +       | +       | +       |
| 0 5 | mcg/ml | +                           | +   | +   | +     | +       | +       | +       |

+ means motile spermatozoa, — means non-motile spermatozoa

tions varying from 10,000 units to 0.01 unit per ml showed numerous actively motile spermatozoa at the end of 51 hours 40 minutes. In concentrations of 10 to 100 units per ml there was a definite increase in the motility. Terramycin in a concentration of 12.5 mg/ml completely immobilized the spermatozoa within 7 minutes, but no lytic changes were detected. In 1.25 mg/ml there was a progressive diminution in the motility of the spermatozoa so that in 4 hours the majority of the spermatozoa were non-motile, and within 15 hours 15 minutes all the spermatozoa were completely non-motile. In concentrations varying from 125 to 0.78 mcg/ml the spermatozoa retained their motility for 4 to 15 hours 15 minutes, but there was a progressive diminution in the motility even though about 5 per cent were still motile in 47 hours 45 minutes. Aureomycin in a concentration of 12.5 mg/ml showed a rapid toxic effect on the motility of the spermatozoa so that in 70 minutes all the spermatozoa were completely non-motile. In a concentration of 1.25 mg/ml there was a gradual reduction in the motility in 3 hours and complete immobility in 17 hours 40 minutes. In a concentration of 125 mcg/ml the motility progressively decreased until all

the spermatozoa were completely non-motile in 21 hours and 40 minutes. In concentrations varying from 12.5 mcg./ml. to 0.78 mcg./ml., Aureomycin had very little effect on spermatozoa in the first 3 hours. In 17 hours 40 minutes there was a gradual diminution in the number of motile spermatozoa even though a few were still motile in 49 hours 40 minutes. Viomycin in a concentration of 25 mg./ml. showed a gradual reduction in the motility of the spermatozoa with complete immobility in 3 hours. In 2.5 mg./ml. all the spermatozoa lost their motility in three and a half hours. In 250 mcg./ml. they were immobilized in 18 hours 45 minutes, and in 25 mcg./ml. all the spermatozoa were non-motile in 27 hours 45 minutes. In 2.5 to 0.125 mcg./ml. a few spermatozoa were still motile at the end of 27 hours and 45 minutes. Most of the spermatozoa survived for a period of 2 to 3 hours in 6.25 mg./ml. Neomycin, but then there was a gradual diminution and complete loss of motility in 18 hours 45 minutes. In 0.625 mg./ml. the progressive diminution in the motility became complete in 24 hours 45 minutes, and in 6.25 and 0.625 mcg./ml. there were still a few motile spermatozoa at the end of 27 hours 45 minutes. Magnamycin in 10 mg./ml. immobilized the spermatozoa in 45 minutes; in 1 mg./ml. in 75 minutes; in 100 mcg./ml. in 3½ hours; in 10 mcg./ml. in 19 hours 40 minutes; in 1 and 0.5 mcg./ml. it had no effect over a period of 27 hours 40 minutes, but in 51 hours 40 minutes all the spermatozoa were completely immobilized. Rimocidin in 1,250 mcg./ml. immobilized the spermatozoa in 20 minutes; in 125 mcg./ml. there was a progressive diminution in the motility and complete fixation in 3 hours; in 12.5 mcg./ml. there was complete immobility in 21 hours 45 minutes; in 1.25 and 0.125 mcg./ml. complete immobility was noticed in 24 hours 40 minutes; and in 0.025 mcg./ml. there were still a few motile spermatozoa at the end of 27 hours 45 minutes. Thiolutin in 1,250 mcg./ml. resulted in immediate fixation and loss of motility of all the spermatozoa. In 125 mcg./ml. the loss of motility was progressive, the spermatozoa were non-motile in 2 hours and 35 minutes. In 12.5 mcg./ml. and 1.25 mcg./ml. they were non-motile in 18 hours 45 minutes, and in 0.125 and 0.0125 mcg./ml. there was progressive loss of motility which resulted in complete immobility in 21 hours 45 minutes. Fumagillin in 1,250 mcg./ml. immediately immobilized all the spermatozoa, in 125 mcg./ml. the loss of motility was progressive and complete in 3 hours. In 12.5 mcg./ml. they were non-motile in 18 hours 45 minutes; in 1.25 mcg./ml. in 24 hours 45 minutes; and in 0.125 and 0.0125 mcg./ml. progressive and complete loss of motility was observed in 24 hours and 45 minutes. Isonicotinic acid hydrazide in 10 mg./ml. showed a gradual loss of motility in 2 hours with complete non-motility in 3 hours. In 1 mg./ml. they were completely non-motile in 21 hours and 45 minutes. In 100 to 0.5 mcg./ml. even though there was a progressive loss of motility, yet at the end of 24 hours and 45 minutes there were still motile spermatozoa.

Table 2 shows that 15 hours after a single injection of 100,000 units of potassium penicillin G, the concentration of the antibiotic in the testis was 0.078, in the liver 0.15, and in the spleen less than 0.78 units per gram. Following 10 injections of 100,000 units penicillin intramuscularly over a 2 week period, the concentration of penicillin in the testis 16 hours after the tenth dose was 0.15

TABLE 1—*Concluded*

|        |        | RIMOCIDIN |     |     |     |      |        |         |        |          |          |          |          |
|--------|--------|-----------|-----|-----|-----|------|--------|---------|--------|----------|----------|----------|----------|
|        |        | 0'        | 20' | 30' | 60' | 101' | 2 hrs. | 2½ hrs. | 3 hrs. | 18½ hrs. | 21½ hrs. | 24½ hrs. | 27½ hrs. |
| 1,250  | mcg/ml | +         | —   | —   | —   | —    | —      | —       | —      | —        | —        | —        | —        |
| 125    | mcg/ml | +         | +   | +   | +   | +    | +      | +       | —      | —        | —        | —        | —        |
| 12.5   | mcg/ml | +         | +   | +   | +   | +    | +      | +       | +      | +        | —        | —        | —        |
| 1.25   | mcg/ml | +         | +   | +   | +   | +    | +      | +       | +      | +        | +        | —        | —        |
| 0.125  | mcg/ml | +         | +   | +   | +   | +    | +      | +       | +      | +        | +        | +        | —        |
| 0.0125 | mcg/ml | +         | +   | +   | +   | +    | +      | +       | +      | +        | +        | +        | +        |

|        |        | THIOLUTIN |     |     |     |      |      |        |          |          |          |          |  |
|--------|--------|-----------|-----|-----|-----|------|------|--------|----------|----------|----------|----------|--|
|        |        | 0'        | 30' | 60' | 90' | 120' | 155' | 3 hrs. | 18½ hrs. | 21½ hrs. | 24½ hrs. | 27½ hrs. |  |
| 1,250  | mcg/ml | —         | —   | —   | —   | —    | —    | —      | —        | —        | —        | —        |  |
| 125    | mcg/ml | +         | +   | +   | +   | +    | +    | —      | —        | —        | —        | —        |  |
| 12.5   | mcg/ml | +         | +   | +   | +   | +    | +    | +      | —        | —        | —        | —        |  |
| 1.25   | mcg/ml | +         | +   | +   | +   | +    | +    | +      | —        | —        | —        | —        |  |
| 0.125  | mcg/ml | +         | +   | +   | +   | +    | +    | +      | +        | —        | —        | —        |  |
| 0.0125 | mcg/ml | +         | +   | +   | +   | +    | +    | +      | +        | —        | —        | —        |  |

|     |        | ISONICOTINIC ACID HYDRAZIDE |     |      |        |          |          |          |  |
|-----|--------|-----------------------------|-----|------|--------|----------|----------|----------|--|
|     |        | 7'                          | 50' | 120' | 3 hrs. | 18½ hrs. | 21½ hrs. | 27½ hrs. |  |
| 10  | mg/ml  | +                           | +   | +    | —      | —        | —        | —        |  |
| 1   | mg/ml  | +                           | +   | +    | +      | +        | —        | —        |  |
| 100 | mcg/ml | +                           | +   | +    | +      | +        | +        | +        |  |
| 10  | mcg/ml | +                           | +   | +    | +      | +        | +        | +        |  |
| 1   | mcg/ml | +                           | +   | +    | +      | +        | +        | +        |  |
| 0.5 | mcg/ml | +                           | +   | +    | +      | +        | +        | +        |  |

+ means motile spermatozoa; — means non-motile spermatozoa.

tions varying from 10,000 units to 0.01 unit per ml. showed numerous actively motile spermatozoa at the end of 51 hours 40 minutes. In concentrations of 10 to 100 units per ml. there was a definite increase in the motility. Terramycin in a concentration of 12.5 mg./ml. completely immobilized the spermatozoa within 7 minutes, but no lytic changes were detected. In 1.25 mg./ml. there was a progressive diminution in the motility of the spermatozoa so that in 4 hours the majority of the spermatozoa were non-motile, and within 15 hours 15 minutes all the spermatozoa were completely non-motile. In concentrations varying from 125 to 0.78 mcg./ml. the spermatozoa retained their motility for 4 to 15 hours 15 minutes, but there was a progressive diminution in the motility even though about 5 per cent were still motile in 47 hours 45 minutes. Aureomycin in a concentration of 12.5 mg./ml. showed a rapid toxic effect on the motility of the spermatozoa so that in 70 minutes all the spermatozoa were completely non-motile. In a concentration of 1.25 mg./ml. there was a gradual reduction in the motility in 3 hours and complete immobility in 17 hours 40 minutes. In a concentration of 125 mcg./ml. the motility progressively decreased until all

the spermatozoa were completely non-motile in 21 hours and 40 minutes. In concentrations varying from 12.5 mcg./ml. to 0.78 mcg./ml., Aureomycin had very little effect on spermatozoa in the first 3 hours. In 17 hours 40 minutes there was a gradual diminution in the number of motile spermatozoa even though a few were still motile in 49 hours 40 minutes. Viomycin in a concentration of 25 mg./ml. showed a gradual reduction in the motility of the spermatozoa with complete immobility in 3 hours. In 2.5 mg./ml. all the spermatozoa lost their motility in three and a half hours. In 250 mcg./ml. they were immobilized in 18 hours 45 minutes, and in 25 mcg./ml. all the spermatozoa were non-motile in 27 hours 45 minutes. In 2.5 to 0.125 mcg./ml. a few spermatozoa were still motile at the end of 27 hours and 45 minutes. Most of the spermatozoa survived for a period of 2 to 3 hours in 6.25 mg./ml. Neomycin, but then there was a gradual diminution and complete loss of motility in 18 hours 45 minutes. In 0.625 mg./ml. the progressive diminution in the motility became complete in 24 hours 45 minutes, and in 6.25 and 0.625 mcg./ml. there were still a few motile spermatozoa at the end of 27 hours 45 minutes. Magnamycin in 10 mg./ml. immobilized the spermatozoa in 45 minutes; in 1 mg./ml. in 75 minutes; in 100 mcg./ml. in 3½ hours; in 10 mcg./ml. in 19 hours 40 minutes; in 1 and 0.5 mcg./ml. it had no effect over a period of 27 hours 40 minutes, but in 51 hours 40 minutes all the spermatozoa were completely immobilized. Rimocidin in 1,250 mcg./ml. immobilized the spermatozoa in 20 minutes; in 125 mcg./ml. there was a progressive diminution in the motility and complete fixation in 3 hours; in 12.5 mcg./ml. there was complete immobility in 21 hours 45 minutes; in 1.25 and 0.125 mcg./ml. complete immobility was noticed in 24 hours 40 minutes; and in 0.025 mcg./ml. there were still a few motile spermatozoa at the end of 27 hours 45 minutes. Thiolutin in 1,250 mcg./ml. resulted in immediate fixation and loss of motility of all the spermatozoa. In 125 mcg./ml. the loss of motility was progressive, the spermatozoa were non-motile in 2 hours and 35 minutes. In 12.5 mcg./ml. and 1.25 mcg./ml. they were non-motile in 18 hours 45 minutes, and in 0.125 and 0.0125 mcg./ml. there was progressive loss of motility which resulted in complete immobility in 21 hours 45 minutes. Fumagillin in 1,250 mcg./ml. immediately immobilized all the spermatozoa, in 125 mcg./ml. the loss of motility was progressive and complete in 3 hours. In 12.5 mcg./ml. they were non-motile in 18 hours 45 minutes; in 1.25 mcg./ml. in 24 hours 45 minutes; and in 0.125 and 0.0125 mcg./ml. progressive and complete loss of motility was observed in 24 hours and 45 minutes. Isonicotinic acid hydrazide in 10 mg./ml. showed a gradual loss of motility in 2 hours with complete non-motility in 3 hours. In 1 mg./ml. they were completely non-motile in 21 hours and 45 minutes. In 100 to 0.5 mcg./ml. even though there was a progressive loss of motility, yet at the end of 24 hours and 45 minutes there were still motile spermatozoa.

Table 2 shows that 15 hours after a single injection of 100,000 units of potassium penicillin G, the concentration of the antibiotic in the testis was 0.078, in the liver 0.15, and in the spleen less than 0.78 units per gram. Following 10 injections of 100,000 units penicillin intramuscularly over a 2 week period, the concentration of penicillin in the testis 16 hours after the tenth dose was 0.15

units per gram. Following 20 injections of 100,000 units penicillin intramuscularly over a four week period the concentration of penicillin in the testis 16 hours after the last dose was 3.0 units per gram. Following 30 injections of 100,000 units penicillin intramuscularly over a 6 week period the concentration of penicillin in the testis and liver 16 hours after the last dose was 0.15 units

TABLE 2. *Penicillin: Testicular levels, effect on weight and spermatogenesis*

|                                                | ANTIBIOTIC LEVEL<br>UNITS/GM.              | WT. OF RAT | SPERMATOGENESIS<br>(MICROSCOPIC FINDINGS IN THE TESTES) |
|------------------------------------------------|--------------------------------------------|------------|---------------------------------------------------------|
| <i>1st determination</i><br>1 × 100,000 units  | Testis 0.078<br>Liver 0.15<br>Spleen <0.78 |            | Fairly normal                                           |
| <i>2nd determination</i><br>10 × 100,000 units | Testis 0.15                                | +3 grams   | Slightly better than fair                               |
| <i>3rd determination</i><br>20 × 100,000 units | Testis 3.0                                 |            | Regular and very good                                   |
| <i>4th determination</i><br>30 × 100,000 units | Testis 0.15<br>Liver 0.15                  |            | Spasmodic, slightly better than normal                  |

TABLE 3. *Polymyxin: Testicular levels, effect on weight and spermatogenesis*

|                                                                                     | ANTIBIOTIC LEVEL<br>UNITS/GM. | WT. OF RAT | SPERMATOGENESIS<br>(MICROSCOPIC FINDINGS IN THE TESTES) |
|-------------------------------------------------------------------------------------|-------------------------------|------------|---------------------------------------------------------|
| <i>1st determination</i><br>1 × 500 units                                           | Testis <2.5<br>Liver <2.5     |            | Normal                                                  |
| <i>2nd determination</i><br>3 × 1,000 units<br>7 × 500 units<br>Total 6,500 units   | Testis <1.9                   | +43 gm.    | Normal and plus                                         |
| <i>3rd determination</i><br>3 × 1,000 units<br>17 × 500 units<br>Total 11,500 units | Testis 0.0                    | +30 gm.    | Very good, same as 20 injections of Terramycin          |
| <i>4th determination</i><br>3 × 1,000 units<br>27 × 500 units<br>Total 16,500 units | Testis <2.5<br>Liver <2.5     | ~50 gm.    | Very good, same as the previous                         |

per gram. There was no appreciable change in the weight of control and penicillin rats. Penicillin has a fair to moderate stimulation of spermatogenesis.

Table 3 shows that 15 hours following a single injection of 500 units polymyxin intramuscularly the concentration in the testis and liver was less than 2.5 units per gram. Sixteen hours after the last dose of 10 injections (3 × 1,000 and 7 × 500, total 6,500 units), the concentration of polymyxin in the testis was less

than 1.9 units per gram; after 20 injections ( $3 \times 1,000$  and  $17 \times 500$ , a total of 11,500 units), no demonstrable polymyxin levels were detected; after 30 injections ( $3 \times 1,000$  and  $27 \times 500$ , a total of 16,500 units) the concentration in the testis and liver was 2.5 units per gram. In the second week the rats put on 43 gm., in the fourth week 30 gm., but in the sixth week there was a loss of 50 gm. in comparison with the normal. The effect of polymyxin on spermatogenesis is quite marked, particularly following 20 injections.

Table 4 shows that 15 hours following a single injection of 1,000 units of bacitracin, the concentration in the testis was 0.12 units per gram, in the liver less than 0.09 units per gram. Sixteen hours following the last dose of 10 injections of 1,000 units the level in the testis was 0.5 units. Nine days after the last dose of 13 injections of 1,000 units, still the testis had 0.5 units per gram. It is signifi-

TABLE 4. *Bacitracin: Testicular levels, effect on weight and spermatogenesis*

|                                                                       | ANTIBIOTIC LEVEL<br>UNITS/GM. | WT. OF RAT | SPERMATOGENESIS<br>(MICROSCOPIC FIND-<br>INGS IN THE TESTES) |
|-----------------------------------------------------------------------|-------------------------------|------------|--------------------------------------------------------------|
| 1st determination<br>1 $\times$ 1,000 units                           | Testis 0.12<br>Liver <0.09    |            | Fair                                                         |
| 2nd determination<br>10 $\times$ 1,000 units                          | Testis 0.5                    | -42 gm.    | Slightly better<br>than fair                                 |
| 3rd determination<br>13 $\times$ 1,000 units (9 days after last dose) | Testis 0.5                    | -52 gm.    | Good                                                         |
| 4th determination<br>animals could not tolerate more than 13<br>doses |                               |            |                                                              |

NB—Extreme local lesions in the skin and muscle with edema and loss of function of extremities due to injection.

cant to note that in 2 weeks the rats lost 42 gm. and in 4 weeks 52 gm. The effect of bacitracin on spermatogenesis was fair or better than fair.

Table 5 shows that 15 hours following a single injection of 10 mg. Magnamycin intramuscularly the concentration in the testis was 0.095 mcg. per gram and in the liver less than 0.095 mcg. per gram. Sixteen hours following the last dose of 10 injections of 10 mg. the concentration in the testis was less than 0.39 mcg. per gram; after 20 injections the concentration in the testis was less than 0.39 mcg. per gram; and in the liver it was 0.39 mcg. per gram. In the first 2 weeks there was an increase of 13 gm. in the weight of the rat while in the fourth week there was a loss of 30 gm. and in the sixth week a loss of 50 gm. The effect of Magnamycin on spermatogenesis is fair or slightly better.

Table 6 shows that 15 hours following a single dose of 10 mg. streptomycin the concentration in the testis was 1.5 units and in the liver 0.312 units per gram. Sixteen hours after the last dose of 10 injections of 10 mg. the concentration in the testis was less than 3.12 units per gram. After 20 injections of 10 mg. the

TABLE 5. *Magnamycin: Testicular levels, effect on weight and spermatogenesis*

|                                  | ANTIBIOTIC LEVEL<br>MCG./GM. | WT. OF RAT | SPERMATOGENESIS (MICROSCOPIC<br>FINDINGS IN THE TESTES) |
|----------------------------------|------------------------------|------------|---------------------------------------------------------|
| 1st determination<br>1 × 10 mg.  | Testis 0.095<br>Liver <0.095 |            | Fair                                                    |
| 2nd determination<br>10 × 10 mg. | Testis <0.39                 | +13 gm.    | Fair, slightly better                                   |
| 3rd determination<br>20 × 10 mg. | Testis 0.312                 | -30 gm.    | Fairly good                                             |
| 4th determination<br>30 × 10 mg. | Testis <0.39<br>Liver 0.39   | -50 gm.    | Fair, not as good as previous one                       |

TABLE 6. *Streptomycin: Testicular levels, effect on weight and spermatogenesis*

|                                  | ANTIBIOTIC LEVEL<br>UNITS/GM. | WT. OF RAT | SPERMATOGENESIS (MICROSCOPIC<br>FINDINGS IN THE TESTES) |
|----------------------------------|-------------------------------|------------|---------------------------------------------------------|
| 1st determination<br>1 × 10 mg.  | Testis 1.5<br>Liver 0.312     |            | Little better than normal                               |
| 2nd determination<br>10 × 10 mg. | Testis <3.12                  | +13 gm.    | Not as good as normal                                   |
| 3rd determination<br>20 × 10 mg. | Testis 6.5                    | +35 gm.    | More regular and normal                                 |
| 4th determination                | Testis <3.12<br>Liver 3.12    | -10 gm.    | Same as normal                                          |

TABLE 7. *Terramycin: Testicular levels, effect on weight and spermatogenesis*

|                                  | ANTIBIOTIC LEVEL<br>MCG./GM. | WT. OF RAT | SPERMATOGENESIS (MICROSCOPIC<br>FINDINGS IN THE TESTES) |
|----------------------------------|------------------------------|------------|---------------------------------------------------------|
| 1st determination<br>1 × 11 mg.  | Testis 0.39<br>Liver <0.39   |            | Normal or less                                          |
| 2nd determination<br>10 × 11 mg. | Testis <1.56                 | +53 gm.    | Close to normal                                         |
| 3rd determination<br>20 × 11 mg. | Testis 1.25                  |            | 2 to 3 times as many spermatozoa                        |
| 4th determination<br>30 × 11 mg. | Testis 0.75<br>Liver 0.75    |            | 2 to 3 times as many spermatozoa                        |

NB—Local reaction to injection.

concentration in the testis was 6.5 units per gram; after 30 injections of 10 mg. of streptomycin, the concentration in the testis was less than 3.12 units and in the liver 3.2 units per gram. The effect on the weight of the rats was an increase

of 13 gm. in 2 weeks, 35 gm. in 4 weeks and a loss of 10 gm. in 6 weeks. Streptomycin had no significant effect on spermatogenesis.

Table 7 shows that 15 hours following a single injection of 11 mg. of Terramycin, the concentration in the testis was 0.39 mcg. per gram and in the liver less than 0.39 mcg. per gram. Sixteen hours following the last dose of 10 injections of 11 mg., the concentration in the testis was less than 1.56 mcg. per gram; after 20 injections of 11 mg., the concentration in the testis was 1.25 mcg. per gram; and after 30 injections of 11 mg., the concentration in the testis and liver was 0.75 mcg. per gram. Microscopic examination of the testis showed a two to three times increase in the number of spermatozoa, indicating that Terramycin apparently had the most marked effect on spermatogenesis.

#### DISCUSSION

The antibiotics which are used in the treatment of various diseases namely; penicillin, streptomycin, Terramycin, Aureomycin, Magnamycin, polymyxin, neomycin and bacitracin show no effect on spermatozoa in therapeutic concentrations and that the survival time ranges between 47 hours 15 minutes to 51 hours 40 minutes.

Bacitracin in 125 to 1,250 units per ml. is definitely toxic to spermatozoa and induces complete lysis within 2 hours. Polymyxin on the other hand in concentrations of 100 to 10 units per ml. increases the motility of the spermatozoa. Thiolutin, fumagillin and Rimocidin in 125 to 1,250 mcg. per ml. immediately immobilize the spermatozoa, but in lower concentrations of 12.5 to 0.0125 mcg. per ml. they immobilize the spermatozoa in 21 to 27 hours. Viomycin in 25, 2.5 and 0.25 mg. per ml. immobilizes the spermatozoa in 3½ hours and 18 hours 45 minutes respectively, but in lower concentrations it does not have any effect. Isonicotinic acid hydrazide immobilizes the spermatozoa in high concentrations namely 10 mg. per ml., but in therapeutic concentrations it has no effect over a period of 27 hours 45 minutes.

A single dose of penicillin, Terramycin, streptomycin, bacitracin, polymyxin or Magnamycin injected intramuscularly into rats in adequate therapeutic doses gave rise to appreciable concentrations in the testis. When multiple injections were given for 2 weeks (10 doses), 4 weeks (20 doses), and 6 weeks (30 doses), there was no significant change in the concentration of polymyxin in the testis, but penicillin, Magnamycin, streptomycin and Terramycin gave rise to a steady increase in the concentration of the respective antibiotic. Bacitracin in 1,000 units per rat weighing 200 gm. was somewhat toxic because the animals could not tolerate more than 13 injections. With this dose in the second week there was a substantial increase in the testicular concentration (0.5 units per gram). There was a cumulative effect with bacitracin in the testis because 9 days following the last injection of 13 doses there was still 0.5 units per gram. The reason why large doses of bacitracin were used was to find out if there was any toxic effect on spermatogenesis, because *in vitro*, bacitracin was reported to be highly toxic to spermatozoa, and in high concentrations it induced lysis of the spermatozoa.<sup>3</sup>



It is apparent from these findings that in bacterial and spirochetal infections of the testes, adequate concentrations of the antibiotics are present in testicular tissue to eradicate the infection.

The most effective antibiotic on spermatogenesis is Terramycin which stimulates the testes to produce two to three times the normal output of spermatozoa. Polymyxin is also very effective but somewhat inferior to Terramycin. Penicillin, bacitracin, and Magnamycin are fairly active in inducing spermatogenesis while streptomycin apparently has very little effect.

Even though these studies are on a limited scale, yet the changes are significant. Further studies are in progress on a more extensive scale concerning the stimulating effect of antibiotics on spermatogenesis, ovulation and menstrual cycle, and will be reported later on.

#### SUMMARY

In therapeutic concentrations the antibiotics which are currently used in the treatment of diseases namely; Terramycin, Aureomycin, penicillin, streptomycin, Magnamycin, polymyxin, bacitracin, neomycin and Viomycin have no effect on the motility of spermatozoa; the survival time in therapeutic concentrations is more than 27 hours 45 minutes with Viomycin and neomycin, and 47 hours 45 minutes to 51 hours 40 minutes with penicillin, streptomycin, Terramycin, bacitracin, polymyxin, Aureomycin and Magnamycin.

Rimocidin, Thiolutin and fumagillin are toxic and the survival time in 0.0125 mcg, per ml. is about 24 hours.

Polymyxin stimulates the motility of the spermatozoa.

Isonicotinic acid hydrazide is non-toxic.

Single dose of penicillin, Terramycin, streptomycin, polymyxin, bacitracin or Magnamycin produces satisfactory therapeutic levels in the testes of rats.

With repeated injections the concentration of the antibiotic in the testes definitely increases except in the case of polymyxin where significant change is not observed.

Bacitracin apparently has a cumulative effect because appreciable concentration is detected in the testes a week following the last dose.

Terramycin, polymyxin, Magnamycin, bacitracin and penicillin have stimulating effect on spermatogenesis.

Terramycin is the most active, increasing the output of spermatozoa by two to three times. Polymyxin is also very effective, while streptomycin has no appreciable effect on spermatogenesis.

Acknowledgement: The authors wish to thank Dr. Meyer M. Melicow, Assistant Professor of Urology, College of Physicians & Surgeons, Columbia University, who examined the sections of the testes.

## THE DEVELOPMENT OF A NEW TESTICULAR PROSTHESIS

CHARLES T. HAZZARD

*From the Squier Urological Clinic, Columbia Presbyterian Medical Center, New York, N. Y.*

Absence of normal testes, whether due to developmental failure or resulting from operative removal, creates a definite sense of inferiority in some individuals. It is not in the scope of this article to consider the psychological aspects of this situation. We will describe the development of a testicular prosthesis, as illustrated in the following case report, which has satisfactorily compensated, cosmetically, for this anatomical deformity.

A patient (P. H. No. 83-90-46), 29 years of age, was admitted to the Squier Urological Clinic August 17, 1946, for repair of a right scrotal hernia. The left testicle had been removed 18 years previously. At operation, August 19, 1946, an atrophic right testicle and rudimentary fallopian tube, proven by biopsy, were located in the peritoneal cavity. It was suspected, preoperatively, that this might be the case, and prompted by the urgent request of the patient, we had provided glass marbles for insertion into the scrotum. Marbles were selected as the least likely of several possible substitutes, available at that time, to produce adverse tissue reaction, and from our standpoint they worked very well. The patient, however, was not satisfied; the marbles were too small. On September 13, 1946, the marbles were removed, embedded in fat secured from his gynecomorphous breasts, and re-implanted in the scrotum. The immediate result appeared to be perfect, but we had been too optimistic. The patient returned to us in April 1952; the fat had been absorbed, the marbles were all that remained. The situation had become quite serious, psychologically, for this man.

Ossacryl, a pure methacrylate, was in use at this time for hip arthroplasty in the Presbyterian Hospital, being manufactured by the Americal Ossacryl Company.\* The company agreed to produce artificial testes to our specifications based on the average weight and size of 100 normal adult testes removed in the Squier Clinic: 4 by 3 by 2.5 cm., 25 gm. (fig. 1).

The first prostheses thus developed were implanted in the scrotum of our patient on April 11, 1952. The accompanying photograph was taken 6 months after operation, and, as demonstrated, the patient has normal-appearing external genitalia (fig. 2). He, personally, is satisfied with the result.

Following orchiectomy for carcinoma of the prostate, these prostheses have been substituted immediately, being fixed in position by snug closure of the tunica vaginalis around the spheres. Primary healing has resulted with no evidence of adverse tissue reaction. Equally satisfactory results have been attained in patients with testicular neoplasm, and with bilateral agenesis of the testes. The prostheses may be stored for long periods, unharmed, in an aqueous solution of 1:1000 zephiran chloride which renders them sterile, and ready for use. They may be boiled, if preferred, but not autoclaved.

Accepted for publication December 24, 1952.  
\* 15 Park Row, New York 58, N. Y.

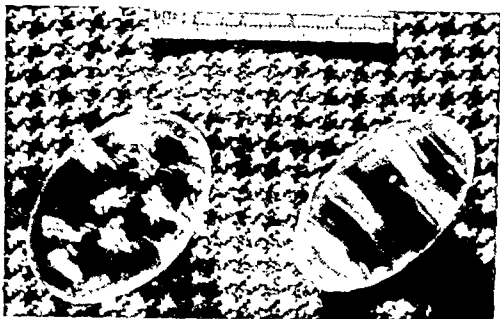


FIG. 1. Frontal and lateral aspects of testicular prostheses.



FIG. 2. Six months after insertion of testicular prostheses in scrotum.

#### SUMMARY

We present a new testicular prosthesis composed of ossacryl, a pure methacrylate, and comparable to the normal adult testicle in size and weight, which has proven to be of value psychologically and cosmetically. We do not advocate the use of the prostheses in all patients undergoing orchiectomy, but we do commend them as a form of substitute therapy in those individuals in whom an absence of testes constitutes a mental barrier to normal living, within their obvious limitations.

*180 Fort Washington Ave., New York 32, N. Y.*

## UNUSUAL SCROTAL ENLARGEMENT IN A CHILD: CASE REPORT

DONALD D ALBERS AND CHARLES M BIELSTEIN

*From the Departments of Urology and Pediatrics, Oklahoma City Clinic and Wesley Hospital Oklahoma City, Oklahoma*

Intrascrotal enlargements are not uncommon in children, but usually consist of hydrocele or hernia. Much less common, but worthy of mention, are enlargements due to epididymitis, orchitis, and torsion of the testicle. Neoplastic diseases of the scrotal contents in children (1 to 15 years of age) are very uncommon. Of the 5,500 testicular tumors reported in the literature up to 1942, only about 1 in 42 occurred in males under 15 years of age.<sup>1</sup> It is generally agreed that most testicular tumors are malignant. Neoplastic disease of the spermatic cord is even less common. While opinion differs appreciably on tumors of the spermatic cord, more recent studies<sup>2</sup> suggest that about 30 per cent of tumors of the spermatic cord are malignant. Although infrequent, enough malignant lesions of the scrotal contents have been reported in children to make the diagnosis a remote possibility.

A cursory review of the literature revealed only one case report of benign cystic lesion of the cord similar to the case to be presented.<sup>3</sup> That was in a 36-year old white male who was found to have a 4 cm smooth lined benign cyst filled with brownish blood-stained fluid lying above a normal testicle and epididymis. A recent very thorough report by Fitzpatrick, et al includes no additional cases.<sup>2</sup> The rarity of the pathological diagnosis warrants documenting this case.

### CASE REPORT

A white boy 6½ years of age was first seen in March 1951 because of an enlargement of the scrotum. Swelling of the right side of the scrotum had been noticed 3 weeks previously, reaching the size of a large orange in a few days. There was some hemorrhagic discoloration of the scrotum and considerable pain. The patient continued to run a low-grade fever and was treated by his local physician with various chemotherapeutic and antibiotic agents. The swelling in the scrotum decreased slowly for about ten days on bed rest and chemotherapy. Nothing was revealed in the history which could possibly have contributed to the enlargement of the scrotum.

The physical examination was noncontributory except for the scrotum. The left testicle and epididymis felt normal. The right scrotum was tense, and a faint bluish color was noted through the thin epidermis. A round, firm, nontender mass 5 cm in diameter with two nodules on its upper border could be felt. The mass did not transilluminate and felt questionably cystic. The laboratory work

Accepted for publication November 25, 1952

<sup>1</sup> Campbell, M. *Clinical Pediatric Urology*. Philadelphia: W. B. Saunders Co., 1951, 1st ed., p. 728.

<sup>2</sup> Fitzpatrick, R. J., Orr, L. M., Clanton, J. B. and Hayward, J. C. *J. A. M. A.*, 148: 259, 1952.

<sup>3</sup> Strong, G. H. *J. Urol.*, 48: 527, 1942.

was essentially noncontributory. Chest x-ray and tuberculin tests were negative. Urinalysis was within normal limits. The white count was 11,950 with a normal differential, and he had mild anemia.

The right scrotum was exposed a few days after admission through a high scrotal and low inguinal incision. In view of the remote possibility of a malignant lesion, the cord was first isolated high and a rubber-shod clamp applied. The scrotal layers were freed from the large bluish mass. A testicle was found deeply imbedded in the upper lateral margin, and when the tunica vaginalis was opened, the testicle, epididymis, and inside of the tunic were entirely normal. The 4 by 5 cm. mass was attached to the inferior medial side of the tunica vaginalis and had rotated and raised the testicle. The tumor was removed intact, leaving the testicle and epididymis undisturbed, but removing some of the parietal tunica vaginalis. When cut open it appeared to be a benign cystic lesion. The rubber-

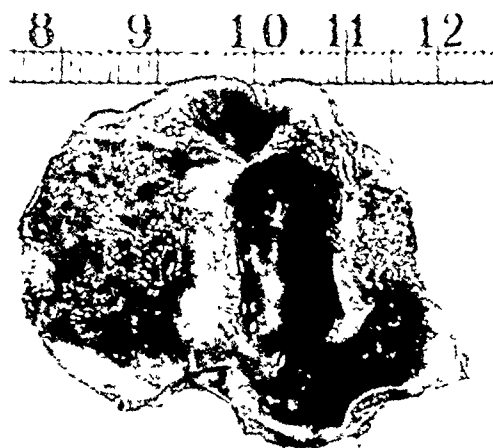


FIG. 1. Showing inner surface of opened three-cavity mass with some old blood adherent to wall.

shod clamp was removed, a bottle operation performed on the testicle, and it was anchored to the bottom of the scrotum. The scrotum was closed and a small drain left in for 24 hours. The postoperative course was entirely uneventful.

The pathologist (Keller) reported on the open specimen which had undergone considerable retraction (fig. 1). "This 4 by 5 cm. specimen consists of three smooth-lined cysts with no epithelial lining which are filled with old blood. The external surface is rough and the wall, 1 by 2 mm. thick, consists of fibrous tissue containing small capillaries, hemosiderinophages and mononuclear inflammatory cells."

This patient was re-examined 9 months following surgery, and the right testicle and epididymis felt normal except for mild thickening of the tissue around the epididymis compatible with the previous surgery.

#### SUMMARY

A case of an extratesticular and extravaginal multiloculated benign cyst of the cord is presented. This apparently represents an unusual reaction to an unexplained hemorrhage in the region of the gubernaculum. No other similar lesion in a child was found in a cursory review of the literature.

## PYELOGRAPHY IN COMBINATION WITH SIMULTANEOUS RETROPERITONEAL PNEUMOGRAPHY

JOHN DUFF, HERBERT R. KENYON AND RICHARD M. HYMAN

*From Department of Urology, Morrisania City Hospital, New York, N. Y.*

The complexity of problems pertaining to lesions of the kidneys and adrenal glands which the urologist is called upon to elucidate is constantly increasing. Consequently improvements in diagnostic methods resulting in more accurate delineations of these organs are eagerly sought for, particularly if they are simple and safe in application. The ultimate potential of pyelography has already been attained. Lumbar arteriography augments the diagnostic armamentarium but is not easy to apply nor wholly free of dangerous consequences.

Demonstration of retroperitoneal structures by air injected directly into the lumbar regions has been practiced for 30 years without achieving general acceptance. First advocated by Carelli and Sordelli, as well as Rosenstein in 1925 and later by Quinby, and Hernaman-Johnson, direct perirenal insufflation was used only occasionally until Cahill, in 1935, modified it and revived interest in the procedure, subsequently reporting on its use in over four hundred cases.

Reports by Mencher, Chevassu and Maingot, Burhans, and Roome commented favorably, but Fish and Weyrauch called attention to the occurrence of embolism which was noted in about 10 per cent of cases. Ajamil, having experienced embolism with paresis and other accidents, stated that the lumbar injection was not suitable for routine use. Mathé emphasized the possibility of embolism. Fatalities have been reported when air or oil are used in tubal insufflation and hysterosalpingography. Modifications such as those of Wilhelm and Barquin relate to technical improvements in radiography but do nothing to minimize the dangers of lumbar insufflation of air.

In summary, many experienced urologists hesitate to use this method even when adrenal disease seems probable. Its disadvantages and dangerous potentialities render it unacceptable. In fact, its employment is prohibited in some clinics.

In addition to the actual hazards, lumbar insufflation presents certain technical disadvantages. The injection must be made into a small, deeply situated space the size and position of which is variable. The needle must penetrate Gerota's fascia. In obese individuals the anatomical landmarks are difficult to identify. The tactile sense governing penetration of the needle is an inexact guide. Separate injections are required on each side for while gas will diffuse from one side to the other (10 per cent of cases according to Senger and Bottone), the resulting films are of little diagnostic value. Distortions of the trunk or of the perinephric space enhance the possibilities of failure and accidents.

We have discarded the direct lumbar route and have adopted the method of

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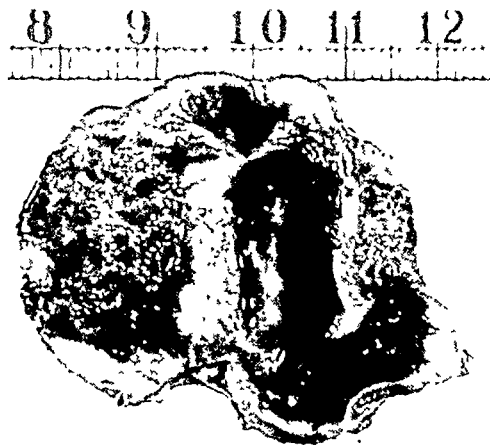


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simultaneous bilateral retroperitoneal emphysema suggested by Rivas in 1950. Used as we suggest, in combination with urographic delineation of the conducting portions of the kidney, the kidneys, adrenals as well as the peri- and paranephric spaces are demonstrated with unusual clarity.

The technique is based upon the fact that all subserous spaces intercommunicate so that emphysema produced in any one area tends to spread to adjacent zones. The retrorectal space is easily penetrated by the needle and is readily accessible. Since ascent of oxygen injected at this point to the retroperitoneal and perinephric spaces is normally free and easy, we consider it the site of election. Our previous anatomical and surgical observations and the reports of Tobin and Benjamin confirm the anatomical factors which, according to Rivas, render the technique feasible. The retrorectal space is avascular, consequently embolism is improbable. It is rarely deformed or obliterated sufficiently to interfere with penetration of the needle. We have yet to encounter an instance in which a proper injection could not be accomplished. The landmark, namely the sacrococcygeal junction on either side, is readily identified even in obese patients.

Preliminary films are exposed and the patient then placed in the knee-chest position. The sacrococcygeal notches are palpated after which, under sterile precautions, a spinal needle is introduced on either side and advanced, just missing the bony edge at the anterior aspect of the inferior border of the sacrum. The direction is medial, posterior and cephalad, following the anterior sacral curve. Penetration of 3-4 cm. brings the needle tip well within the retrorectal space. Anesthesia is unnecessary.

Resistance is not encountered during the insertion of the needle. A source of oxygen is connected by way of a three-way stopcock to the needle and a 50 cc Luer syringe. Oxygen is safer than either air or helium. The first increment is injected slowly. While force is not required there is an appreciable although slight resistance as the syringe is emptied. Complete absence of resistance suggests penetration into the rectal lumen. If actual force is required, the position of needle should be readjusted, permitting a more even and easier flow. Manual manipulation of the syringe is most important. Mechanical devices cannot transmit perception to the consciousness of the operator.

Provided the first increment enters properly, the syringe is rapidly filled and emptied. In the average adult we have found 1,250 cc the optimum quantity. The age, size and stature of the patient provide criteria for varying the total quantity. Larger volumes do not necessarily improve the quality of the films. Fullness in the epigastrium or loins does not contra-indicate completion of the injection but suggests that the gas is diffusing properly. The rate of injection has no regular relation to the quality of films and we now inject the total amount as rapidly as possible. When the needle is withdrawn, the patient assumes a sitting position, flexing the trunk several times to facilitate dispersion of the gas. A 14 by 17 film is exposed and, if the pneumogram is satisfactory, we proceed immediately with a retrograde or intravenous urogram, the former being the method of choice unless cystoscopy is contra-indicated. Delayed, oblique films, tomograms, etc. are taken as indicated. Supplementary arteriography can be used if desired.

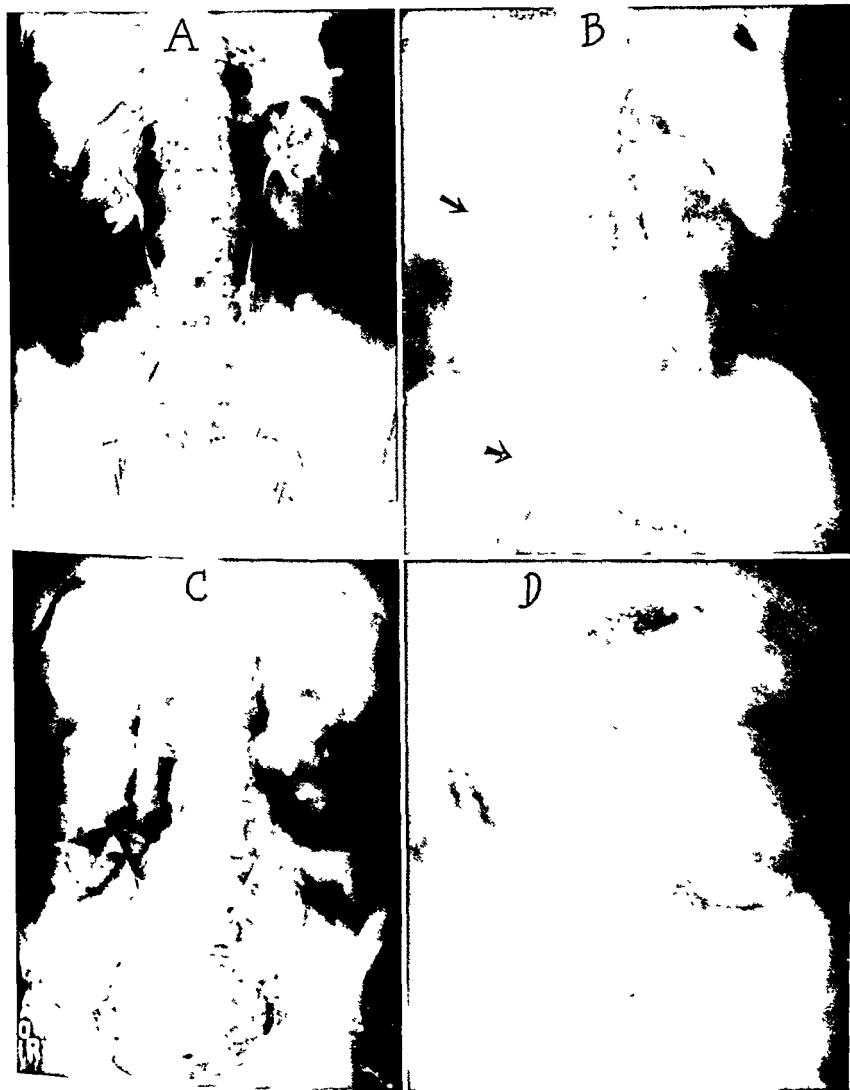


FIG. 1. *A*, normal pyclopneumogram. Retrorectal oxygen insufflation is combined with retrograde pyelography. Oxygen well distributed revealing normal perirenal outlines and pyelogram within normal limits. Both adrenals well outlined and normal in size, shape and position. *B*, oblitative perinephritis, right. Excellent pneumogram of hypertrophied left kidney. Leaf of diaphragm and spleen are particularly well delineated. Diffusion is absent on right. Case of proven extensive perinephritis secondary to long standing calculous disease in pelvis and ureter (see arrows). *C*, bilateral polycystic disease. Insufflation combined with excretory urography. Pneumogram reveals extensive irregular and lobulated perirenal outlines and size of both kidneys is easily evaluated. *D*, large cyst of left lower pole. Oxygen insufflation reveals large, spherical, well outlined left renal contour. Retroperitoneal spaces distorted by kyphoscoliosis.

This type of pneumography appears to be innocuous. There have been no disturbing complications. In 2 cases the needle penetrated the rectum without ill effect. Emphysema of the abdominal wall was observed three times, disap-



FIG. 2. *A*, ectopic right pelvic kidney. Normal left pyelopneumogram. Thin rim of oxygen surrounds ectopic kidney (arrow). Gas diffuses into retroperitoneal space on right, but usual fascial anatomy and structures are present. *B*, perinephritis and peri-ureteritis, right. Because of inflammatory obliteration of right perirenal space, no oxygen diffuses. On left, complete normal pyelopneumogram. *C*, perinephric abscess, right. Case of proven extensive perinephric abscess. Complete absence of oxygen diffusion on right. Left pneumogram is excellent and reveals sharply delineated adrenal gland (see arrow). *D*, perirenal space obliterated following surgery. Postoperative adhesions and scarring are present in obliteration of right perirenal space. Some oxygen, however, diffuses outside Gerota's fascia mesial to kidney and along psoas margin. Pneumogram on left very sharp and normal showing well defined conical adrenal gland (arrow).

pearing in a few hours. Fullness in the loins and epigastrium is common, but transitory. Mild substernal pressure with slight dyspnea was recorded twice and 2 cases of cervical and one of scrotal emphysema occurred.

The age limits of over 150 patients were 4 and 73 years, with 8 patients under 12 years, twenty were age 70 or older. The pulse and blood pressure were unaffected during and for one half hour after completion of the injection. Pneumograms can be repeated after the lapse of 48 hours when necessary. The average time involved in completing the injection was 4 minutes, including the insertion of the needle. Pronounced discomfort, severe pain or syncope was not observed in our series.

Clear renal and adrenal outlines are usually obtained bilaterally in normal individuals. Anomalous or pathological conditions which prevent diffusion of the gas result in incomplete or complete failure to outline these structures. The shadows are not always uniform and, while the adrenals are ordinarily clearly shown, the lines of demarcation between them and the kidneys are sometimes indistinct. Minor changes in adrenal configuration may be difficult to diagnose, necessitating repetition of insufflation or surgical exploration, when indicated, for final diagnosis.

Failure of gaseous diffusion is significant and is attributable to congenital defects, adhesions resulting from inflammation or previous surgery and neoplastic invasion of pericystic, peri-ureteral or perinephric tissues.

Renal ectopia, renal agenesis and similar anomalies cause coincident deviations in the retroperitoneal fascial planes. Repeated failure to demonstrate these structures is evidence of deformity or disease and coincides with our previous anatomical and surgical observations.

Co-incident pneumography and pyelography establish the thickness of the renal cortex. Renal and retroperitoneal masses are more readily distinguished from masses arising in the liver, spleen or other intraperitoneal organs. We have demonstrated changes associated with solitary kidneys, polycystic disease, solitary cyst, retrocaval ureter, ectopic pelvic kidney, horseshoe kidney and renal neoplasm as well as massive hydronephrosis, extension of papillary tumors of the pelvis, retroperitoneal metastases from testicular neoplasm and a miscellany of comparable conditions. Evidences of pathologic changes such as obliteration of the perinephric and paranephric spaces derived from pneumographic studies provide indications for the type of therapy chosen and the selection of the operative approach. This small series could not include examples of all renal and adrenal lesions.

We have observed exceptionally clear outlines of the perivesical spaces in a number of pneumograms and are now investigating its utility as a method of determining whether a vesical neoplasm has infiltrated beyond the adventitia of the bladder.

#### SUMMARY

Integrated urography and retroperitoneal pneumography by the retrorectal route is a safe and informative diagnostic procedure. The concurrent use of both

procedures enhances the diagnostic possibilities to an extent that is unobtainable when either method is used alone and at a separate time.

An appreciation of the commonly encountered variants has been fairly well established. Criteria for the more accurate diagnosis of certain renal, adrenal and retroperitoneal lesions are now available. The method is particularly applicable to the differential diagnosis of retroperitoneal tumors. More complete exploitation of this method requires further correlation of the radiographic with surgical and post-mortem observations.

Its inherent diagnostic possibilities encourage the belief that it will prove increasingly valuable with continued use.

*745 Fifth Ave., New York, N. Y.*

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## THE DORSAL CYSTOGRAM OR "SQUAT SHOT": A TECHNIQUE FOR ROENTGENOGRAPHY OF POSTERIOR BLADDER AND PELVIC URETERS

WILLIAM H. BOYCE, JAMES A. HARRIS AND SAMUEL A. VEST

*From the Department of Urology, University of Virginia Hospital, Charlottesville, Va.*

The satisfactory x-ray delineation of the dorsal (posterior) area of the bladder, the region adjacent to the trigonum, and the retrovesical portions of the ureters is not always obtainable by the standard technique of anteroposterior, oblique and lateral positions. The density of the pelvic bones, the sacrum, the femur, and the acetabulum occasionally makes adequate x-ray exposures difficult or impossible. Ureteral reflux, bladder diverticula, and other pathologic lesions may be completely obscured by these bony prominences or by the overlying shadow of the cystogram.

The following technique for x-ray exposure of the bladder was proven a valuable "scout" film for cystography and has demonstrated pathologic changes which would not be visualized by any of the other methods. The patient's position for this x-ray exposure was first described by Chassard and Lapine<sup>1</sup> as a method for obtaining measurements of the female pelvis, and more recently by Raap<sup>2</sup> as a method for roentgenography of the rectum and pelvic colon. The following variations in the Chassard-Lapine technique have proven applicable to any type of cystoscopic table and x-ray tube commonly used in urologic practice.

### METHOD

The bladder is filled with contrast solution (250 cc of 15 per cent analytical grade sodium iodide) in the usual manner. The cassette containing the x-ray film (11 by 14 inches) is placed cross-wise in the Bucky tray and the patient then asked to sit upright on the cystoscopic table and dangle his legs over the side. He is instructed to grasp his ankles and to lean as far forward as possible so that he literally sits over the film (fig. 1). The x-ray tube is adjusted directly over the center of the pelvis and a dorsal-caudal exposure made. Since the distance is usually fixed at 30 inches for the average cystoscopic table, we have found an exposure of 200 Ma. at 85 KVP for 1 to 2 seconds to be adequate for most patients. For x-ray tubes in which less milliamperage is desirable a distance of 30 inches and an exposure of 100 Ma. at 80 KVP for 5 seconds will give comparable results. The exposed film is developed and if any pathologic deformity is observed, the routine anteroposterior, oblique, and lateral exposures may then be made as indicated. By tilting the table until the patient is semi-erect, a voiding cysto-urethrogram may be obtained as the final exposure.

With the patient in this "squatting" position the central ray passes through the center of the bony pelvis along the posterior margin of the trigonum vesicae.

Accepted for publication November 4, 1952.

<sup>1</sup> Chassard and Lapine: *J. radiol. et electrol.*, 7: 113-124, 1923.

<sup>2</sup> Raap, Gerard: *South. Med. J.*, 44: 95-98, 1951.

The dome of the bladder is tilted forward and the posterior surface of the bladder and retrovesical ureters exposed. This position thus exposes those portions of the bladder which are most often subject to pathologic changes of the type demonstrable by cystography. Only the anterior bladder wall and the anterior vesical neck are partially obscured, areas which are rarely the sites of either diverticula or tumors.

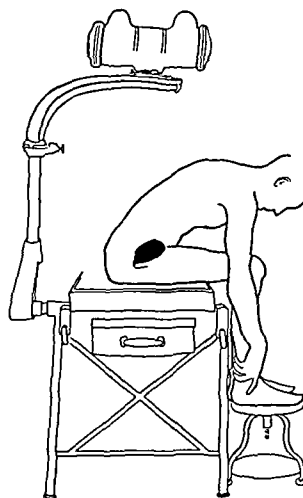


FIG. 1. Position for "squat shot." Fundus of bladder is tilted forward and central ray passes parallel to posterior margin of trigonum.

TABLE 1. Comparison of routine\* and squat cystograms in 33 patients

| CYSTOGRAPHIC DEFORMITY   | ROUTINE   |                    |                       |              | SQUAT              |
|--------------------------|-----------|--------------------|-----------------------|--------------|--------------------|
|                          | Not Shown | Incompletely Shown | Shown Equally As Well | Shown Better | Shown in All Cases |
| Diverticula, 19 cases    | 5         | 12                 | 2                     | 0            | 19                 |
| Ureteral reflux, 8 cases | 2         | 1                  | 3                     | 2            | 8                  |
| Tumor, 6 cases           | 3         | 1                  | 2                     | 0            | 6                  |
| Total                    | 10        | 14                 | 7                     | 2            | 33                 |

\* Routine cystograms include anteroposterior, obliques, and lateral films.

#### RESULTS

This technique has been applied to 65 patients in addition to those exposures routinely used in cystography. Twenty-two of these had normal bladders; 10 had generalized pathologic changes such as cellulitis, atonic dilatation, etc.; and 33 had specific pathologic changes such as diverticula, ureteral reflux or tumor. In this group of 43 patients with generalized or specific pathologic conditions of the bladder, we found that the dorsal cystogram gave unmistakable evidence of the pathologic change in 100 per cent. The pathologic change was demonstrated by the dorsal cystogram and not by any one of the anteroposterior, lateral, or oblique exposures in 10 of the 33 patients with specific pathologic

deformities of the bladder. It was our impression that these supplemental anteroposterior, lateral, and oblique films did not give any information of clinical value in addition to that obtained from the dorsal cystogram in 94 per cent of these 33 patients (table 1). The remaining 6 per cent were 2 individuals with uretero-renal reflux of unusual degree.

Figure 2, *A* demonstrates the visualization of a large diverticulum arising from the posterior wall and two smaller diverticula arising from either lateral



FIG. 2. Three diverticula of bladder, *A*, squat shot. One large posterior diverticulum and two small lateral diverticula are clearly demonstrated. *B*, anteroposterior view (voiding). Same patient *A*. Diverticula are incompletely demonstrated. *C*, right oblique view. Large diverticulum is illustrated but relationship to bladder cannot be accurately demonstrated. Diverticula were less well demonstrated on left oblique and lateral films.



FIG. 3. Intravesical protrusion of prostatic adenoma with two bladder diverticula. *A*, squat shot. Filling defect caused by protrusion of median lobe of prostate into bladder. Two large diverticula are present on right bladder wall. Note clear delineation of "neck" of each diverticulum. *B*, anteroposterior view. Same patient as *A*. There is suggestion of single diverticulum on right. Intravesical adenoma not demonstrated. *C*, right oblique view. Diverticula obscured by cystogram and adenoma not demonstrated. Neither intravesical adenoma nor diverticula were demonstrated on left oblique or lateral films.

bladder wall as shown by the dorsal exposure. This is compared with the incomplete visualization of these diverticula as shown by the routine anteroposterior (fig. 2, *B*) and right oblique (fig. 2, *C*) x-ray exposures. These films were made in as rapid succession as the patient could be positioned on the table.

Figure 3, *A* illustrates the intravesical protrusion of a prostatic adenoma with two large vesical diverticula by the dorsal technique as compared with the anteroposterior (fig. 3, *B*) and oblique (fig. 3, *C*) exposures. A different type of intravesical tumor (benign papilloma) arising from a pedicle just mesial to the right intramural ureter is illustrated by the "squat shot" (fig. 4, *A*) as compared with



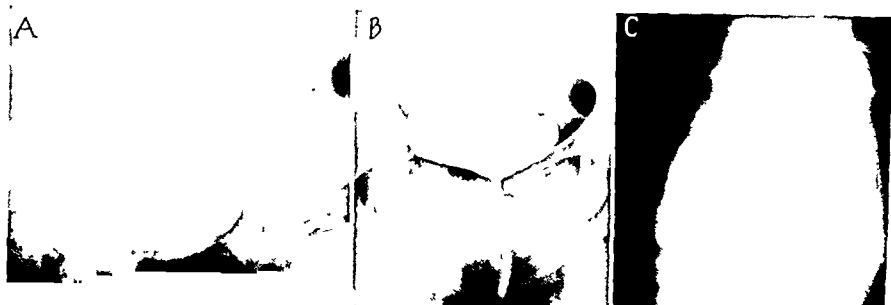


FIG. 4. Intravesical tumor (papilloma). *A*, squat shot. Note accurate localization of tumor (filling defect) in region of right intramural ureter. *B*, anteroposterior view. Tumor is obscured by volume of contrast material between anterior and posterior bladder walls. *C*, view. Same patient as *A*. Overlying bony prominences and tissue density result in poor contrast between cystogram and surrounding structures. Tumor was very poorly shown on right oblique and not at all on left oblique films.



FIG. 5. Bilateral ureteral reflux in patient with sacral meningocele. *A*, squat shot. Bilateral ureteral reflux demonstrates partial reduplication of right ureter. Involuntary voiding resulted in cystogram of small size. *B*, Anteroposterior view. Same patient as *A*. Ureteral reflux not demonstrated, possibly because intravesical pressure in supine position is less than in "squat" position. Thus latent reflux may be demonstrated by squat and not by other x-ray positions.

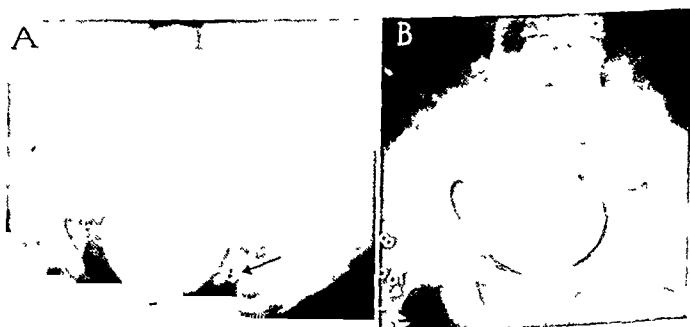


FIG. 6. Left ureteral reflux in patient with physiologically incomplete transection of cervical cord. *A*, squat shot. Note reflux (arrow) into retrovesical segment of left ureter (X-ray opaque catheter is in urethra) *B*, anteroposterior view. Same patient as *A*. Ureteral reflux obscured by cystogram. Reflux was not demonstrated on oblique and lateral films.

the incomplete visualization on the anteroposterior (fig. 4, *B*) and lateral (fig. 4, *C*) exposures.

Neurogenic reflux of the contrast material into the ureters of a young adult

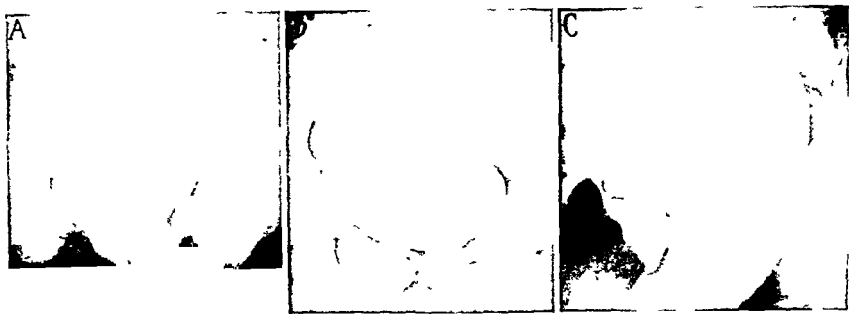


FIG. 7. Reflux into residual ureteral stump following left nephrectomy and partial ureterectomy. *A*, squat shot. Position of extravascular contrast material is unmistakably within region of left ureteral stump. *B*, anteroposterior view. Same patient as *A*. Ureteral reflux is obscured by cystogram. *C*, right oblique view. Same patient as *A*. Note impossibility of accurately localizing extravascular contrast material in relation to trigone or ureter. Reflux was not demonstrated on left oblique or lateral films

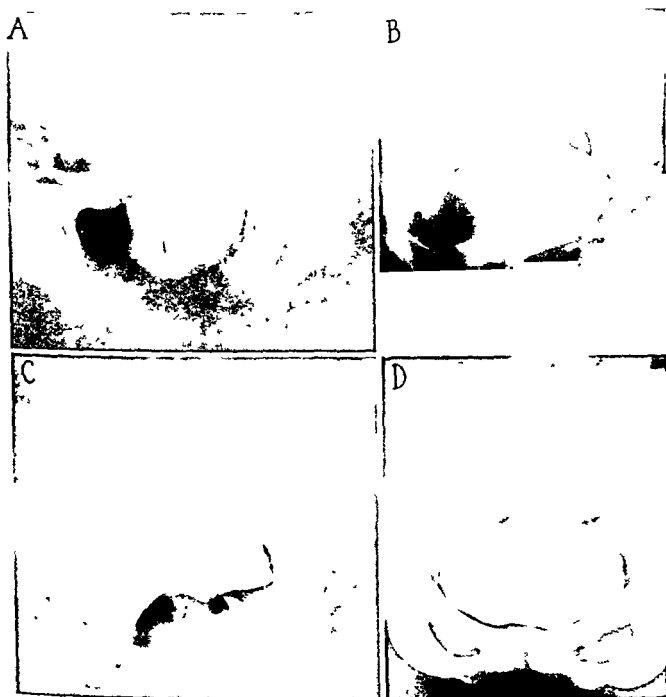


FIG. 8. *A* and *B*, intra-abdominal tumor (fibromyomas of uterus) *A*, squat shot. Note extrinsic pressure causing filling defect of right side and displacement of bladder to left. (X-ray opaque catheter is within the left ureter) *B*, anteroposterior view. Same patient as *A*. *C* and *D*, extravascular intrapelvic tumor (sarcoma) *C*, squat shot. Note filling defect in region of left posterior bladder wall and trigone with slight "ballooning" of right posterior bladder wall. *D*, anteroposterior view. Same patient as *C*. Deformity shown in *C* is not demonstrated. Pathologic change was not demonstrated on oblique or lateral films.

female with congenital meningocele is demonstrated in figure 5, *A*, as compared with the routine anteroposterior film (fig. 5, *B*). This illustrates the anatomical curvature of the retrovesical ureters and demonstrates how 5 to 8

cm. of the ureter may be obscured by the bladder shadow on an anteroposterior cystogram. Ureteral reflux not demonstrated in the supine position may be accentuated by the "squat" position, as in this case, possibly because of increased intrapelvic and intravesical pressure. Such reflux was not demonstrated in any of the 22 normal patients. The occult ureteral reflux that may occur in neurogenic dysfunction is illustrated in figure 6, *A*. This patient had a compression fracture of the fourth cervical vertebra with resultant quadraplegia 2 years prior to the time this cystogram was made. Recovery had been sufficient to permit ambulation on crutches but there was a residual neurogenic dysfunction of the bladder.

Mechanical reflux into the remaining stump of the ureter following nephrectomy and partial ureterectomy is illustrated by figure 7, *A*. This was not demonstrated on the anteroposterior (fig. 7, *B*) and lateral cystograms and was incompletely visualized on the oblique cystogram (fig. 7, *C*).

Extravesical tumors which impinge upon the bladder wall are demonstrated by figure 8. Figure 8, *A* illustrates the distortion of the cystogram by an abdominal tumor (multiple adenoleiomyofibromas of the uterus). Figure 8, *C* demonstrates the distortion of the posterior portion of the bladder by a large pelvic tumor (sarcoma).

#### SUMMARY AND CONCLUSIONS

Thirty-three of 65 patients subjected to cystography were found to have ureteral reflux, diverticula, or tumor involving the bladder. These pathologic changes were unmistakably demonstrated by the single "squat shot" in 100 per cent of the 33 cases, as compared with only 66 per cent demonstration of these changes by any one of the anteroposterior, oblique, or lateral views. Furthermore, the information obtained from these latter "routine" views was considered to be of additional clinical value in only 2 of the 33 patients, both of whom had ureterorenal reflux.

It is concluded that the dorsal cystogram ("squat shot") may be used as a single "screening" film for suspected pathologic deformity of the bladder, thus eliminating the large number of films required for cystography by conventional methods.

*Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.*  
(*W. H. B.*)

## CIRCULATORY COLLAPSE FOLLOWING COMBINED USE OF RAYOPAKE AND AIR FOR URETHROCYSTOGRAPHY

KENNETH A. FORBES AND JUSTIN J. CORDONNIER

*From the Urological Service, Veterans Administration Hospital, Jefferson Barracks, Mo. and the Department of Surgery, Washington University School of Medicine, St. Louis, Mo.*

Since the introduction of Rayopake (formerly called Visco-Rayopake) for hysterosalpingography in 1941, and later for urethrography, a number of favorable reports<sup>1-5</sup> on its clinical application have reached the literature. This contrast medium has been shown to be of superior quality from a radiographic standpoint and to date there have been no published reports of serious untoward reactions following its use. In his preliminary report, Rubin<sup>1</sup> summarized the toxic properties of this radiographic medium as investigated by Koppányi and his associates. The findings were corroborated by his own experimental work. Lespinasse's<sup>5</sup> investigations were in accord with those of Koppányi's and Rubin's. However, he warned against its use in the central nervous system. Richards<sup>3</sup> proclaimed Rayopake to be "the safest and most efficient urethrographic contrast medium yet produced." In a recent paper on cysto-urethrography Boone<sup>9</sup> apparently found Rayopake to be a satisfactory contrast substance since there was no mention of unusual reactions to the medium.

The injection of air into the bladder, as a contrast medium for cystography or to facilitate cystoscopy and surgical procedures, has been condemned because of the possibility of air embolism. Mathé<sup>10</sup> emphasized this danger in a comprehensive article in 1929. He included in his report several instances of air embolism occurring during urethroscopy when air was used to dilate the urethra. In 1933, Flocks<sup>11</sup> suggested the combined use of an air cystogram and an opaque urethrogram for study of the lower urinary tract.

Presented with permission of the Chief Medical Director, Division of Medicine and Surgery, of the Veterans Administration who assumes no responsibility for the opinions expressed by the authors.

Accepted for publication December 5, 1952.

<sup>1</sup> Rubin, I. C.: New soluble viscous contrast medium for hystero-graphy: Preliminary report. *J. Mt. Sinai Hosp.*, 7: 479, 1941.

<sup>2</sup> Goldberger, N. A.: The clinical evaluation of hystero-graphy. *J. Mt. Sinai Hosp.*, 10: 241, 1943.

<sup>3</sup> Bernstein, P.: Hysterosalpingography, a routine aid in gynecological diagnosis. *Am. J. Obst. & Gynec.*, 48: 189, 1944.

<sup>4</sup> Norment, W. B.: The use of a new contrast medium (Visco-Rayopake) in the female generative tract. *Am. J. Obst. & Gynec.*, 49: 253, 1945.

<sup>5</sup> Lespinasse, V. D.: Urethrograms of the male urethra. *Quart. Bull., Northwestern Univ. M. School*, 19: 298, 1945.

<sup>6</sup> Coe, F. O. and Arthur, P. S.: A new medium for cysto-urethrography. *Am. J. Roentgenol.*, 56: 361, 1946.

<sup>7</sup> Brodny, M. L. and Robins, S. A.: The use of a new viscous water-miscible contrast medium Rayopake for cysto-urethrography. *J. Urol.*, 58: 182, 1947.

<sup>8</sup> Richards, C. E.: Visco-Rayopake in cysto-urethrography. *J. Urol.*, 58: 185, 1947.

<sup>9</sup> Boone, A. W.: Cysto-urethrograms before prostatectomy. *J. Urol.*, 67: 358, 1952.

<sup>10</sup> Mathé, C. P.: Fatal embolus due to inflation of bladder with air. *Surg., Gynec. & Obst.*, 48: 429, 1929.

<sup>11</sup> Flocks, R. H.: The roentgen visualization of the posterior urethra. *J. Urol.*, 30: 711, 1933.

Hyams,<sup>12</sup> in discussing Flocks' paper, called attention to the possibility of air embolism with the use of this method.

The purpose of this paper is to report a nearly fatal shock-like state which followed the instillation of Rayopake into the urethra while the bladder contained a moderate amount of air.

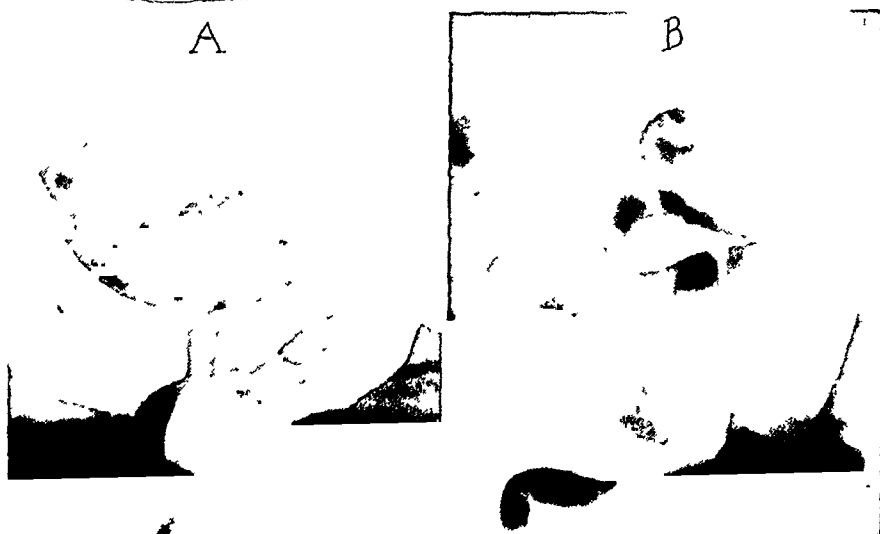


FIG. 1

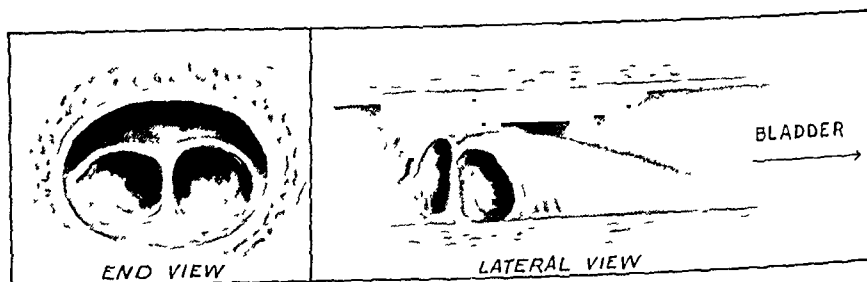


FIG. 2

#### CASE REPORT

A 60 year old white man was referred to the urological service because of suprapubic pain and pyuria believed to be due to a vesicosigmoidal fistula. There were no obstructive urinary symptoms. The findings on physical examination were within normal limits. On routine catheterization for residual urine a partial obstruction was encountered in the anterior urethra.

Urethroscopy revealed a membranous structure which extended transversely across the floor of the anterior urethra approximately two centimeters distal to the external urethral sphincter. The membrane appeared to be about 2 millimeters in thickness, one centimeter long and formed a blind pocket which was

<sup>12</sup> Hyams, J. A · Ibid.

divided into two parts by a vertical membranous fold extending from the transverse septum to the floor of the urethra (figs. 1 and 2). There was slight encroachment on the prostatic urethra by the left lateral lobe of the prostate.

Cystoscopy revealed a chronically inflamed bladder with a fungating mass on the left posterolateral wall. Cystoscopic biopsy of the mass was done later on two occasions and both specimens showed chronic inflammation on histopathologic examination.

Because of the unusual nature of the membranous structure in the anterior urethra, urethrograms were made in a manner similar to the method of Flocks, using Rayopake. Approximately 150 cc air was gently injected through a catheter into the bladder with a syringe. After removal of the catheter, 30 cc Rayopake was instilled into the urethra and exposures made in the anteroposterior and right oblique positions during the installation. It should be mentioned at this point that Flocks introduces air into the bladder just to the point of fullness and withdraws 30 cc after the pneumocystogram exposure has been made, and before the contrast medium has been injected. This is presumably a precaution against air embolism.

After the two films had been exposed and while the Rayopake was draining from the urethra, the patient complained of urethral burning and dizziness and his face and neck were noted to be flushed. This was followed by coughing and expectoration. A period of apnea of 30 seconds' duration then occurred after which irregular, labored respirations were noted. Cyanosis rapidly appeared. The patient's head was lowered, he was given positive-pressure oxygen from an anesthesia machine and an intravenous injection of 240 mg. of aminophylline on the presumption that bronchospasm was present. During the injection a generalized clonic convulsion occurred which subsided after 30 seconds and was followed by hyperirritability for approximately five minutes. This responded readily to 90 mg. sodium amytal intravenously. The blood pressure and pulse were unobtainable. The patient was then given 1 cc of 1:1000 epinephrine and 50 mg. of ephedrine intramuscularly while a liter of 10 per cent glucose in water was started as an intravenous infusion until plasma could be prepared. After the administration of 750 cc plasma, and 10 mg. neosynephrine dissolved in the 10 per cent glucose solution, the blood pressure was obtained at 90 systolic, 60 diastolic and the pulse at 128 per minute. The patient's color and vital signs gradually improved and he was returned to his ward with a blood pressure of 105 systolic, 70 diastolic, a pulse of 90 per minute and respirations of 28 per minute. He was in shock for approximately 1 hour.

The patient required supportive therapy on the ward for an additional 6 hours before his vital signs stabilized. During this period he vomited twice and defecated involuntarily once. His urinary output was low for the next 24 hours but became normal thereafter. For several days he was lethargic and confused, had involuntary urination and defecation and complained of impaired vision. These residuals of cerebral hypoxia gradually cleared within 2 weeks. Skin tests for iodine sensitivity were performed with Rayopake, Diodrast and Skiodan. All gave a negative response.

## COMMENT

It is impossible to state with certainty the exact cause of this patient's severe reaction since only clinical findings are available for evaluation. Two possible explanations are, of course, anaphylactoid reaction to the iodine-containing Rayopake or air embolism from the air-containing bladder. A combination of the two phenomena, while theoretically possible, would seem unlikely. Any attempt to analyze the factors in this case for the purpose of ascribing the patient's symptoms and signs to one or the other possibility would be purely conjectural.

The principal agent responsible for allergic reactions to urographic media is usually considered to be the organic iodine compound.<sup>13</sup> Rayopake is described as a viscous, aqueous solution containing 50 per cent diethanolamine salt of 2,4-dioxo-3-iodo-6-methyl-tetrahydro-pyridine-N-acetic acid and 4.8 per cent polyvinyl alcohol, with 0.01 per cent benzalkonium chloride as preservative. The iodine content is approximately 15 per cent (weight/volume). It is claimed by the manufacturer to be rapidly absorbed from the urethra. Despite this ability for rapid absorption, no serious reactions definitely attributable to Rayopake have been reported.

The fact that the patient gave no personal or family history of allergic diseases and had tolerated intravenous Diodrast used for excretory urography two weeks earlier is of interest. Allergic phenomena are still incompletely understood, however, and, although some authorities do not believe that true anaphylaxis exists in man, it is entirely possible that the first organic iodine solution (Diodrast) acted as the sensitizing dose and the second (Rayopake) as the provocative dose. It is to be noted that no Rayopake can be seen entering the pelvic veins (figs. 1 and 2), indicating that any absorption which might have occurred to produce a reaction, was, indeed, small in quantity. Skin tests are usually negative in the drug-sensitive individual regardless of whether the allergy is of the hereditary or acquired form.<sup>14</sup>

The severe vasomotor collapse, the smooth muscle stimulation manifested by bronchospasm and increased gastro-intestinal activity, the generalized clonic convulsions and loss of anal and urethral sphincter control exhibited by the patient have been described in reports on experimental anaphylaxis<sup>15</sup> and in instances of drug reactions in humans.<sup>13</sup> Urticarial manifestations may be absent in a given case.<sup>15, 16</sup>

A perusal of the literature on air embolism will reveal that the clinical features of this form of embolism in some cases closely resemble those seen in anaphylactoid reactions. A shock-like state is described with loss of sphincter control, vomiting, convulsions, visual disturbances and mental lethargy, the severity depending upon the amount and distribution of the air within the cardiovascu-

<sup>13</sup> Pendergrass, E. P., Chamberlin, G. W., Godfrey, E. W. and Burdick, E. D.: A survey of deaths and unfavorable sequelae following the administration of contrast media. *Am. J. Roentgenol.*, **48**: 741, 1942.

<sup>14</sup> Traub, S. J.: *Clinical Allergy*. New York: Paul B. Hoeber, 2nd ed., 1951, pp. 161, 162.

<sup>15</sup> Everett, R.: Anaphylactic reactions from local use of penicillin. *J.A.M.A.*, **146**: 1314, 1951.

<sup>16</sup> Burleson, R. J.: Anaphylactoid shock due to penicillin. *J.A.M.A.*, **142**: 562, 1950.

lar system. It is apparent, then, that when a diagnostic procedure is utilized which carries the risk, however remote, of either of these reactions, it will be difficult, if not impossible, to arrive at a correct diagnosis on the basis of the clinical findings alone.

The membranous structure described in the anterior urethra was interpreted as a congenital malformation since the patient gave no history of urethral disease or instrumentation in the past. It offered no obstruction to the flow of urine but interfered with the retrograde passage of urethral instruments and the retrograde flow of Rayopake. The increased pressure required to overcome the obstruction is believed to have been a factor in precipitating the reaction in this individual either by increasing the absorption rate of the iodine compound or by forcing air into the veins of the inflammatory mass (vesicosigmoidal fistula) in the bladder.

Since the exact cause of the shock in this patient cannot be determined and in view of the factors outlined in the foregoing paragraphs, it would seem wise to abandon the introduction of air into the urethra or bladder for any purpose and to exercise caution when injecting an iodine compound into the urethra in the presence of an obstructive lesion.

#### SUMMARY

A severe shock-like reaction following the combined use of Rayopake and air for urethrocytography in a 60 year old man is described. The patient, who gave no history of previous allergic diseases, was undergoing a urologic examination for suspected vesicosigmoidal fistula. During the examination a congenital anterior urethral membrane was found and demonstrated by urethrograms. The exact cause of the reaction could not be determined after recovery of the patient. It is speculated, however, that the increased pressure required to overcome the obstruction offered by the membrane was a factor in provoking it either by increasing the absorption rate of the iodine-containing Rayopake resulting in an anaphylactoid reaction or by forcing air into the veins of the vesicosigmoidal fistula to produce air embolism. The injection of air into the urethra or bladder for any reason is not recommended and the injection of an iodine-containing medium through an obstructed urethra should be done with caution.



## COMMENT

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<sup>14</sup> Traub, S. J.: *Clinical Allergy*. New York: Paul B. Hoeber, 2nd ed., 1951, pp. 161, 162.

<sup>15</sup> Everett, R.: Anaphylactic reactions from local use of penicillin. *J.A.M.A.*, **146**: 1314, 1951.

<sup>16</sup> Burleson, R. J.: Anaphylactoid shock due to penicillin. *J.A.M.A.*, **142**: 562, 1950.

room and yields at the same time urethrograms of the same quality as that obtained from using the old technique of inserting the bulb syringe directly into the urethra.

#### TECHNIQUE

A Cunningham penis clamp is loosely applied behind the glans penis. The penis is then grasped with the left hand, and up to 15 cc of 20 per cent Skiodan is slowly injected into the meatus of the urethra by a bulb syringe until resistance is noted. With the tip of the bulb syringe still held firmly in the meatus in order to prevent leakage, the Cunningham clamp is closed. The bag is then attached

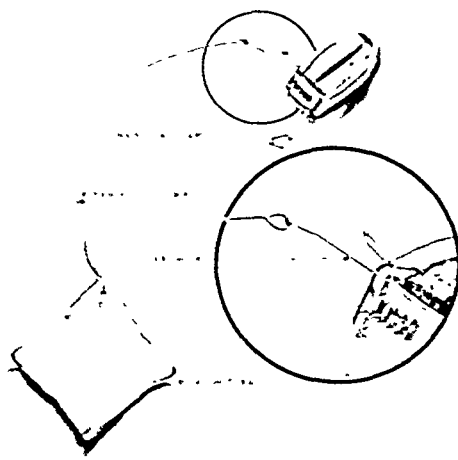


FIG 2. Materials necessary for safe, simple technique

to the Cunningham clamp by means of a hook, and is hung over the edge of the cystoscopy table with the penis in transverse position, as described previously by one of us (A. E. C.).<sup>2</sup> Pictures are then taken in the supine and oblique positions (fig. 1).

The items needed are: 1) A bag of lead shot weighing approximately 375 gm.; 2) a 12 inch length of flexible stainless steel wire; 3) a copper wire hook and) a Cunningham clamp. The materials are readily available and the only expense is the Cunningham clamp (fig. 2).

#### SUMMARY

An inexpensive method of performing urethrograms is presented which combines excellent pictorial results with full safety for the technician from any exposure to x-rays.

## A SAFE, SIMPLE METHOD OF PERFORMING URETHROGRAMS

A. ESTIN COMARR AND LAMBERT DODENHOFF

*From the Paraplegia Service of Veterans Administration Hospital, Long Beach, Calif. and the Department of Surgery-Urology, School of Medicine, University of California at Los Angeles*

Urethrography is a well recognized method in general urology and has become even more important for the urologic management of paraplegic patients who tend to develop quite frequently diverticula or sinus tracts at the penoscrotal junction.<sup>1,2</sup> Urethrography has become of necessity a diagnostic pro-



FIG. 1. Showing patient in oblique position with penis in transverse plane. Lead shot bag is suspended over edge of cystoscopy table.

cedure with such patients which is carried out on admission and regularly spaced check-up examinations.

The only drawback of urethrography is the danger from roentgen overexposure to the technician. In order to reduce this hazard we tried the Brodny clamp.<sup>3</sup> Yet, aside from the fact that we were not too successful with that technique, it still kept the technician in the room within the range of x-rays. The following method, created by our chief-technician (L. D.), eliminates the danger of exposure to x-rays for the technician by screening him completely from the

<sup>1</sup> Comarr, A. E.. Urethral pathology in paraplegic patients. Paper delivered before the So. Calif. Chapter, Am. Coll Surg, Riverside, Calif. on January 20, 1951.

<sup>2</sup> Comarr, A. E. and Bors, Ernest. Pathological changes in urethra of paraplegic patients. *J. Urol.*, **66**: 355-361, 1951.

<sup>3</sup> Brodny, M. L.: A new instrument for urethrography in the male. *J. Urol.*, **46**: 351-352, 1941.

room and yields at the same time urethrograms of the same quality as that obtained from using the old technique of inserting the bulb syringe directly into the urethra.

### TECHNIQUE

A Cunningham penis clamp is loosely applied behind the glans penis. The penis is then grasped with the left hand, and up to 15 cc of 20 per cent Skiodan is slowly injected into the meatus of the urethra by a bulb syringe until resistance is noted. With the tip of the bulb syringe still held firmly in the meatus in order to prevent leakage, the Cunningham clamp is closed. The bag is then attached

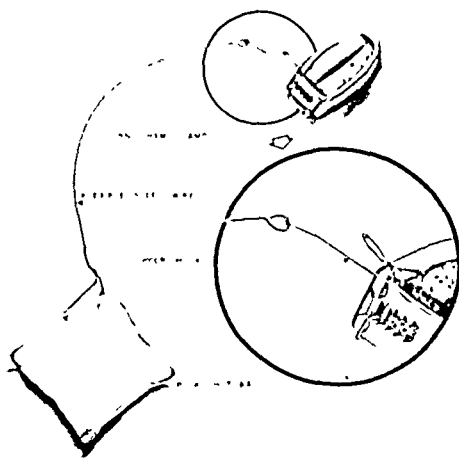


FIG. 2. Materials necessary for safe, simple technique

to the Cunningham clamp by means of a hook, and is hung over the edge of the cystoscopy table with the penis in transverse position, as described previously by one of us (A. E. C.).<sup>1, 2</sup> Pictures are then taken in the supine and oblique positions (fig. 1).

The items needed are: 1) A bag of lead shot weighing approximately 375 gm.; 2) a 12 inch length of flexible stainless steel wire; 3) a copper wire hook and a Cunningham clamp. The materials are readily available and the only expense is the Cunningham clamp (fig. 2).

### SUMMARY

An inexpensive method of performing urethrograms is presented which combines excellent pictorial results with full safety for the technician from any exposure to x-rays.

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